of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

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FILE 'HOME' ENTERED AT 07:41:14 ON 02 AUG 2007

=> file emdline embase biosis biotechds scisearch hcaplus ntis lifesci
'EMDLINE' IS NOT A VALID FILE NAME
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available. If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.
ENTER A FILE NAME OR (IGNORE):medline

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 07:41:51 ON 02 AUG 2007

FILE 'EMBASE' ENTERED AT 07:41:51 ON 02 AUG 2007
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FILE 'HCAPLUS' ENTERED AT 07:41:51 ON 02 AUG 2007
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FILE 'NTIS' ENTERED AT 07:41:51 ON 02 AUG 2007
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FILE 'LIFESCI' ENTERED AT 07:41:51 ON 02 AUG 2007
COPYRIGHT (C) 2007 Cambridge Scientific Abstracts (CSA)

=> s "shc"
L1 12209 "SHC"

=> s sh3 (w)domain
L2 17027 SH3 (W) DOMAIN

=> s l1 and l2
L3 588 L1 AND L2

=> s "MAPKAP2 kinase?" or "MK2"
L4 2640 "MAPKAP2 KINASE?" OR "MK2"

=> s l3 and l4
L5 0 L3 AND L4

=> s mapkap####
L6 2372 MAPKAP####

```
=> s l3 and l6
L7            1 L3 AND L6

=> d ibib ab

L7   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2005:121193  HCAPLUS
DOCUMENT NUMBER:          142:214836
TITLE:                    Biomarkers of cyclin-dependent kinase modulation in
                          cancer therapy
INVENTOR(S):              Li, Martha; Rupnow, Brent A.; Webster, Kevin R.;
                          Jackson, Donald G.; Wong, Tai W.
PATENT ASSIGNEE(S):       Bristol-Myers Squibb Company, USA
SOURCE:                   PCT Int. Appl., 141 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2005012875         A2    20050210    WO 2004-US24424         20040729
     WO 2005012875         A3    20070315
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG
     AU 2004262369         A1    20050210    AU 2004-262369          20040729
     CA 2533803            A1    20050210    CA 2004-2533803         20040729
     EP 1656542            A2    20060517    EP 2004-779471          20040729
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR
     JP 2007507204         T     20070329    JP 2006-522045          20040729
     US 2007105114         A1    20070510    US 2006-567867          20060818
PRIORITY APPLN. INFO.:                       US 2003-490890P      P  20030729
                                             WO 2004-US24424      W  20040729
```

AB Biomarkers having expression patterns that correlate with a response of cells to treatment with one or more cdk modulating agents, and uses thereof. Transcription profiling was used to identify the biomarkers. Specifically, transcription profiling of the effect of a certain cdk2 inhibitor (BMS 387032 0.5 L-tartaric acid salt) on peripheral blood mononuclear cells was first performed. Gene chips were used to quantitate the levels of gene expression on a large-scale with Affymetrix human gene chips HG-U95A, B, and C. Next, profiling of a cdk2 inhibitor-treated tumor cell line A28780 at multiple doses and time points was performed to establish a correlation of tumor site response with peripheral blood biomarkers. In order to establish the mol. target-specificity of the potential biomarkers, tumor cell line A2780 treated with anti-cdk2 oligonucleotides was also profiles. Overlapping gene expression changes were selected for further evaluation in human ovarian carcinoma xenograft A2780 that were treated with the cdk2 inhibitor. The selected biomarkers were subjected to real-time PCR anal. in order to verify the observed changes from the gene chip anal. The biomarker comprising GenBank accession number W28729 was discovered to have the most consistent and robust regulation in response to cdk inhibition. Provided are methods for testing or predicting whether a mammal will respond therapeutically to a method of

treating cancer that comprises administering an agent that modulates cdk activity.

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=> d his

     (FILE 'HOME' ENTERED AT 07:41:14 ON 02 AUG 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 07:41:51 ON 02 AUG 2007
L1         12209 S "SHC"
L2         17027 S SH3 (W)DOMAIN
L3           588 S L1 AND L2
L4          2640 S "MAPKAP2 KINASE?" OR "MK2"
L5             0 S L3 AND L4
L6          2372 S MAPKAP####
L7             1 S L3 AND L6

=> s l1 and l4
L8             5 L1 AND L4

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9             2 DUP REM L8 (3 DUPLICATES REMOVED)

=> d 1-2 ibib ab

L9    ANSWER 1 OF 2  BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
      DUPLICATE 1
ACCESSION NUMBER: 2004-09118  BIOTECHDS
TITLE:            New isolated, purified or recombinant protein complex
                  comprising an MK2 polypeptide, and an MK2
                  interacting protein chosen from STS, HPH2 and Shc
                  for treating or preventing e.g. Crohn's disease, or
                  rheumatoid arthritis;
                     involving vector-mediated gene transfer and expression in
                     host cell for use in gene therapy
AUTHOR:           LIN L; YANNONI Y M
PATENT ASSIGNEE:  WYETH
PATENT INFO:      WO 2004012660 12 Feb 2004
APPLICATION INFO: WO 2003-US23981 1 Aug 2003
PRIORITY INFO:    US 2002-400044 2 Aug 2002; US 2002-400044 2 Aug 2002
DOCUMENT TYPE:    Patent
LANGUAGE:         English
OTHER SOURCE:     WPI: 2004-156998 [15]
AB    DERWENT ABSTRACT:
      NOVELTY - An isolated, purified or recombinant protein complex comprising
      a mitogen-activated protein kinase-activated protein kinase 2 (
      MK2) polypeptide, and an MK2 interacting protein chosen
      from STS, HPH2 and Shc, is new.
           DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the
      following: (1) a host cell comprising a first and a second nucleic acid,
      where the first nucleic acid encodes a recombinant MK2
      polypeptide and the second nucleic acid encoding MK2
      interacting protein; (2) an assay for determining whether the test
      compound inhibits or promotes formation of a protein complex; (3) a
      method for determining whether a test compound affects MK2
      activity; (4) an screening assay to identify compounds that inhibit or
      promote formation of the protein complex; (5) an antibody that binds one
      or more proteins in the complex; (6) a method for modulating formation of
      a protein complex in a cell comprising at least a first and a second
      protein; (7) a method for producing a complex; (8) a drug screening
      method for identifying anti-inflammatory drugs; (9) a method of
      modulating inflammation in a tissue; (10) a method of treating or
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preventing inflammation in a tissue; (11) a method of treating a patient suffering from at least one inflammatory condition; (12) a method of expressing a nucleic acid in a cell to inhibit inflammation; (13) a method of detecting at least one of the absence, presence and amount of MK2 in a sample; (14) a kit that enables qualitative detection of MK2 comprising a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and at least one other kit component chosen from: at least one of buffer and solution; and at least one structural component; and (15) a pharmaceutical composition comprising at least one protein that binds MK2, and at least one carrier.

BIOTECHNOLOGY - Preferred Complex: The protein complex comprises an MK2 polypeptide and at least one or two MK2 interacting protein. The MK2 interacting protein is chosen from STS, HPH2 and Shc. The MK2 polypeptide comprises a fusion protein. The fusion protein comprises a domain for purifying, isolating or detecting the fusion protein. The fusion protein comprises a domain chosen from affinity tags, radionucleotides, enzymes, and fluorophores. The domain is selected from polyhistidine, FLAG, Glu-Glu, glutathione S transferase (GST), thioredoxin, protein A, protein G, and an immunoglobulin heavy chain constant region. Preferred Method: Determining whether a test compound inhibits or promotes formation of a protein complex comprises forming a reaction mixture including an MK2 polypeptide, at least one MK2 interacting protein and the test compound; and detecting the presence of the protein complex between MK2 and the MK2 interacting protein, where a difference in the amount of complex in the presence of the test compound, relative to the amount of complex in the absence of the test compound indicates that the test compound inhibits or promotes complex formation. An increase in the amount of complex in presence of the test compound indicates that the test compound promotes complex formation. A decrease in the amount of complex in presence of the test compound indicates that the test compound inhibits complex formation. Determining whether a test compound affects MK2 activity comprises forming a protein complex comprising an MK2 polypeptide and an MK2 interacting protein; contacting the protein complex with the test compound; and determining the effect of the test compound on one or more activities chosen from MK2 kinase activity, an amount of MK2 in the complex, production of TNF, and amount of phosphorylated form of a substrate of MK2. The screening assay to identify compounds that inhibit or promote formation of a protein complex, comprises providing a two-hybrid assay system including a first fusion protein comprising an MK2 polypeptide, and a second fusion protein comprising a polypeptide chosen from one or more of STS, HPH2 and Shc, under conditions where the two proteins interact in the two hybrid assay system; measuring a level of interaction between the fusion proteins in the presence and in the absence of a test compound; and comparing the level of interaction of the fusion proteins, where a decrease in the level of interaction is indicative of a compound that inhibits the interaction between the MK2 polypeptide and a polypeptide chosen from one or more of STS, HPH2 and Shc. Modulating formation of a protein complex in a cell comprising at least a first protein and a second protein, where the first protein is an MK2 polypeptide and the second protein is chosen from one or more of STS, HPH2 and Shc, comprises administering to the cell a compound capable of modulating formation of the complex. Producing a complex comprises transfecting a cell with one or more polynucleotides encoding an MK2 polypeptide and an MK2 interacting protein chosen from one or more of STS and Shc, where the polypeptides form a complex. The drug screening method for identifying anti-inflammatory drugs comprises providing MK2 and at least one MK2-interacting protein; allowing MK2 and the protein to interact to form a complex; adding an effective amount of a

potential drug to the complex; and determining whether the potential drug inhibits complex formation. The MK2 and the protein interact in vivo in a yeast or mammalian 2-hybrid system. The MK2 and the protein interact in vitro. The protein is STS, Shc or HPH2. The drug is a small molecule, peptide or protein, antibody, or chemical agent. Modulating inflammation in a tissue comprises administering a nucleic acid that encodes an MK2 interacting protein to the tissue; and allowing the nucleic acid to express the MK2 interacting protein, thus to modulate inflammation in the tissue. The nucleic acid expresses a protein chosen from STS, HPH2 and Shc. Treating or preventing inflammation in a tissue comprises administering to the tissue a therapeutically effective amount of at least one agent that blocks the interaction between MK2 and an MK2 interacting protein; or allows the interaction, but blocks MK2 activity. The agent is an antibody, preferably a polyclonal or monoclonal antibody. The antibody binds MK2 or the MK2 -interacting protein. The agent is a chemical agent, a peptide or protein, or a small molecule. Modulating inflammation in a tissue comprises contacting the tissue with at least one protein that binds MK2; and allowing the protein to modulate inflammation in the tissue. Treating a patient suffering from at least one inflammatory condition, comprises administering a therapeutically effective dose of at least one compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the compound to bind to at least one of MK2 or an MK2 complex and modulate inflammation. The protein or peptide is a mutant form of a wild-type protein or peptide, which stimulates MK2 activity. Expressing a nucleic acid in a cell to inhibit inflammation comprises adding at least one nucleic acid encoding a compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the cell to express the compound and inhibit inflammation. Detecting at least one of the absence, presence, and amount of MK2 in a sample, comprises administering at least one compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and correlating the absence, presence, or amount of bound protein or compound with the absence, presence, or amount of MK2 in the sample. Preferred Antibody: The antibody inhibits interaction of MK2 with the MK2 interacting protein. Preferred Kit: The kit further comprises an agent that binds the protein or compound. The agent is an antibody.

ACTIVITY - Antiinflammatory; Gastrointestinal; Antiarthritic; Antirheumatic; Respiratory-Gen; Antiasthmatic; Immunosuppressive; Antiulcer. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The composition and methods are useful for treating or preventing a condition chosen from Crohn's disease, inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, acute respiratory distress syndrome, emphysema, delayed type hypersensitivity reaction, asthma, systemic lupus erythematosus, and inflammation due to trauma or injury (claimed).

ADMINISTRATION - Dosage is 5-500, preferably 40-60 mg per kg. Administration is intravenous, intramuscular, rectal or subcutaneous.

EXAMPLE - Experimental protocols are described but no results are given. (107 pages)

L9 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004196650 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15094067
TITLE: P66(ShcA) interacts with MAPKAP kinase 2 and regulates its

activity.
AUTHOR: Yannoni Yvonne M; Gaestel Matthias; Lin Lih-Ling
CORPORATE SOURCE: Department of Inflammation, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140-2311, USA..
yvonne.yannoni@abbott.com
SOURCE: FEBS letters, (2004 Apr 23) Vol. 564, No. 1-2, pp. 205-11.
Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20 Apr 2004
Last Updated on STN: 4 Jun 2004
Entered Medline: 3 Jun 2004

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66(ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation.

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=> d his

     (FILE 'HOME' ENTERED AT 07:41:14 ON 02 AUG 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 07:41:51 ON 02 AUG 2007
L1         12209 S "SHC"
L2         17027 S SH3 (W)DOMAIN
L3           588 S L1 AND L2
L4          2640 S "MAPKAP2 KINASE?" OR "MK2"
L5             0 S L3 AND L4
L6          2372 S MAPKAP####
L7             1 S L3 AND L6
L8             5 S L1 AND L4
L9             2 DUP REM L8 (3 DUPLICATES REMOVED)

=> s "shc#"
L10       12209 "SHC#"

=> s kinase(w) binding (W)domain?
L11         312 KINASE(W) BINDING (W) DOMAIN?

=> s l1 and l11
L12           6 L1 AND L11

=> dup rem l12
PROCESSING COMPLETED FOR L12
L13           1 DUP REM L12 (5 DUPLICATES REMOVED)

=> d ibib ab

L13  ANSWER 1 OF 1     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:   2001426026     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 11375397
TITLE:              Cbl-b-dependent coordinated degradation of the epidermal
                    growth factor receptor signaling complex.
```

AUTHOR: Ettenberg S A; Magnifico A; Cuello M; Nau M M; Rubinstein Y R; Yarden Y; Weissman A M; Lipkowitz S

CORPORATE SOURCE: Genetics Department of the Medicine Branch and the Laboratory of Immune Cell Biology, Center for Cancer Research, NCI, National Institutes of Health, Bethesda, Maryland 20889, USA.

SOURCE: The Journal of biological chemistry, (2001 Jul 20) Vol. 276, No. 29, pp. 27677-84. Electronic Publication: 2001-05-24.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200108

ENTRY DATE: Entered STN: 27 Aug 2001
Last Updated on STN: 5 Jan 2003
Entered Medline: 23 Aug 2001

AB Cbl proteins function as ubiquitin protein ligases for the activated epidermal growth factor receptor and, thus, negatively regulate its activity. Here we show that Cbl-b is ubiquitinated and degraded upon activation of the receptor. Epidermal growth factor (EGF)-induced Cbl-b degradation requires intact RING finger and tyrosine kinase binding domains and requires binding of the Cbl-b protein to the activated EGF receptor (EGFR). Degradation of both the EGFR and the Cbl-b protein is blocked by lysosomal and proteasomal inhibitors. Other components of the EGFR-signaling complex (i.e. Grb2 and Shc) are also degraded in an EGF-induced Cbl-b-dependent fashion. Our results suggest that the ubiquitin protein ligase function of Cbl-b is regulated by coordinated degradation of the Cbl-b protein along with its substrate. Furthermore, the data demonstrate that Cbl-b mediates degradation of multiple proteins in the EGFR-signaling complex.

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=> d his

     (FILE 'HOME' ENTERED AT 07:41:14 ON 02 AUG 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
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L1         12209 S "SHC"
L2         17027 S SH3 (W)DOMAIN
L3           588 S L1 AND L2
L4          2640 S "MAPKAP2 KINASE?" OR "MK2"
L5             0 S L3 AND L4
L6          2372 S MAPKAP####
L7             1 S L3 AND L6
L8             5 S L1 AND L4
L9             2 DUP REM L8 (3 DUPLICATES REMOVED)
L10        12209 S "SHC#"
L11          312 S KINASE(W) BINDING (W)DOMAIN?
L12            6 S L1 AND L11
L13            1 DUP REM L12 (5 DUPLICATES REMOVED)

=> s l4 and (proline (w)rich)
L14           13 L4 AND (PROLINE (W) RICH)

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15            3 DUP REM L14 (10 DUPLICATES REMOVED)

=> d 1-3 ibib ab

L15   ANSWER 1 OF 3  BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
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ACCESSION NUMBER: 2004-16816 BIOTECHDS
TITLE: Novel isolated mitogen activated protein kinase activated protein kinase polypeptides, useful as therapeutic agents in treating inflammatory based diseases;
involves crystallization of the recombinant protein and the use of bioinformatic software in ligand identification
AUTHOR: PARRIS K D; UNDERWOOD K W; STAHL M L; MOSYAK L; SVENSON K; SHANE T; TAYLOR M L
PATENT ASSIGNEE: PARRIS K D; UNDERWOOD K W; STAHL M L; MOSYAK L; SVENSON K; SHANE T; TAYLOR M L
PATENT INFO: US 2004091872 13 May 2004
APPLICATION INFO: US 2002-294027 13 Nov 2002
PRIORITY INFO: US 2002-294027 13 Nov 2002; US 2002-294027 13 Nov 2002
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2004-410434 [38]

AB DERWENT ABSTRACT:
NOVELTY - An isolated mitogen activated protein kinase (MAP) activated protein kinase 2 (MK2) polypeptide (I) having an amino acid sequence corresponding to portion of MK2, in which the N-terminus begins at amino acid 41-55 and the C-terminus ends at 338 to 365, or its analog, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a nucleic acid (II) encoding (I); (2) a vector (III) comprising (II); (3) a transformed host cell (IV), transfected or infected with (III);(4) producing (I); (5) obtaining (M1) a crystallized native MK2, crystallized MK2 polypeptide or crystallized MK2 analog, involves contacting native MK2, MK2 polypeptide or MK2 analog with a buffer solution comprising at least one of cacodylate, Tris, Tris-HCl, acetate, malonate, sodium phosphate, potassium phosphate, citrate, N-(2-hydroxyethyl)piperazine-N'-ethanesulfonic acid (HEPES) and MES, at a salt concentration of 0.1 M-2.4 M and at a pH of 4.5 to 8.5, under conditions permitting the formation of crystallized MK2, crystallized MK2 polypeptide or crystallized MK2 analog; (6) a crystallized complex (V) of MK2 polypeptide and staurosporine, having four molecules of MK2 polypeptide in the asymmetric unit; (7) a crystallized complex (VI) of MAP polypeptide and ADP, having one molecule of MK2 polypeptide in the asymmetric unit; (8) a three dimensional model (VII) of MK2, defined by the relative structural coordinates for molecules A, B, C or D of MK2, a portion of molecules A, B, C or D of MK2, molecule A of MK2 or a portion of a molecule A of MK2, +/- a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5 Angstrom; (9) an active site of MK2 (VIII), comprising the relative structural coordinate of amino acid residues Leu70, Gly71, Leu72, Gly73, Val78, Ala91, Val118, Met138, Glu139, Cys140, Leu141, Glu145, Glu190, Asn191, Leu192, Thr206 and Asp207 of molecules A, B, C or D, or Ile74, Asn75, Lys93 of molecule A of MK2, +/- root mean square deviation from the backbone atoms of the amino acids of not more than 1.5 Angstrom; (10) identifying (M2) an agent that interacts with MK2, involves generating a three-dimensional model of MK2 using the relative structural coordinates of molecules A, B, C or D of MK2, portion of molecules A, B, C or D of MK2, molecule A of MK2 or a portion of molecule A of MK2, +/- root mean square deviation from the backbone atoms of the amino acid of not more than 1.5 Angstrom, and employing the three-dimensional model to identify an agent that interacts with MK2; (11) designing (M3) a putative agent that interact with an active site of MK2, involves generating a three dimensional model of the active site using the relative structural coordinates of amino acid residues (A1) Val69, Ile74, Gly76, Ala77, Leu79, Gln80, Lys89, Phe90, Leu92, Lys93, Leu95, Glu104, His108, Arg119, Ile136, Val137, Asp142, Gly143, Gly144, His184, Asp186, Lys188, Pro189, Leu193, Tyr194, Thr195, Lys204, Leu205, Phe208

and Gly209 of molecules A, B, C or D of MK2, +/- a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5 Angstrom, and designing a putative agent that interacts with the active site by performing computer fitting analysis of the putative agent with the three-dimensional model generated; (12) identifying (M4) a putative agent that interacts with an active site of MK2, involves generating a three-dimensional site using of MK2 using the relative structural coordinates of amino acid residues Leu70, Gly71, Leu72, Gly73, Val78, Ala91, Val118, Met138, Glu139, Cys140, Leu141, Glu145, Glu190, Asn191, Leu192, Thr206 and Asp207 of molecules A of MK2, +/- root mean square deviation from the backbone atoms of the amino acid of not more than 1.5 Angstrom, and designing a putative agent that interacts with the active site by performing computer fitting analysis of the putative agent with the three dimensional model generated; and (13) an agent (IX) identified by (M2), (M3) or (M4).

BIOTECHNOLOGY - Preparation: Producing (I), involves transforming, transfecting or infecting (IV), and culturing (IV) under conditions permitting the production of (I) (claimed). Preferred Polypeptide: (I) has an amino acid sequence corresponding to amino acids 41-364 of MK2 or its analog. Preferred Method: In (M1), the salt has an anion such as sulfate, citrate, chloride, acetate, phosphate, malonate and tartrate. The salt concentration is 0.8 M or higher. The native MK2, MK2 polypeptide or MK2 analog is contacted with the buffer solution in the presence of polyethylene glycol (PEG) or PEG substitute (PEG-200, PEG-400, PEG-500-MME, PEG-1000, PEG-1500, PEG-2000-MME, PEG-3350, Jeffamine M-600, ethylene glycol, glycerol and 1-6 hexanediol, 2-methyl-2,4-pentanediol (MPD), preferably PEG-400), having a molecular weight up to 3350. (M2) further involves obtaining the identified agent, and contacting the identified agent with MK2 in order to determine the effect the agent has on MK2 activity. (M3) and (M4) further involves obtaining the agent designed, and contacting the agent with MK2 in the presence of staurosporine and ADP in order to determine the effect the agent has on inhibiting binding between MK2 and staurosporine and ADP, respectively. Preferred Complex: (V) has a space group P63, unit cell parameters of a=b=160.20 Angstrom, c = 133.48 Angstrom. (VI) has a space group F4132, unit cell parameters of a=b=c=253.05 Angstrom. Preferred Model: In (VII), the +/- root mean square deviation from the backbone atoms of the amino acids is not more than 1.0 Angstrom or 0.5 Angstrom. Preferred Active Site: (VIII) further comprises the relative structural coordinates for amino residues (A1), and amino acid residues (AA1) Met94, Glu145, Glu190, Leu193 and Phe210 of molecule A or MK2, +/- a root mean square deviation from the backbone atoms of the amino acid of not more than 1.5 Angstrom, 1.0 Angstrom or 0.5 Angstrom.

ACTIVITY - Antiinflammatory.

MECHANISM OF ACTION - Modulator of MK2. Ni biological data given.

USE - (I) and (IX) are useful as therapeutic agents in treating inflammatory based diseases.

EXAMPLE - Mitogen activated protein kinase activated protein kinase polypeptide (MAPKAP)kinase 2 gene was PCR cloned into the NcoI and XhoI sites of pET16b using Hot tub polymerase. The expressed protein contained residues 41-364, excluding the N-terminal proline-rich sequence. To produce selenomethionine labeled MK2, the protein was expressed in BL21 (DE3) Escherichia coli at 25 degreesC. Precultures were grown in shake flasks in LeMaster media supplemented with L-methionine and expression cultures were grown in LeMaster media supplemented with L-selenomethionine that was replenished upon culture induction. Cultures were induced with 0.5 mM isopropyl-beta-D-thiogalactoside (IPTG) for 4 hours. Unlabeled MK2 was also expressed in E. coli BL21 (DE3). The culture was induced with 0.5 mM IPTG and cells were harvested 4 hours post-induction, and purified. MK2 41-364 was crystallized over a broad pH range (4.5 to 8.5). MK2 was crystallized using a variety of buffers (Cacodylate,

Tris, Tris-HCl, Acetate, Malonate, Sodium/Potassium phosphate, Citrate, N-(2-hydroxyethyl)piperazine-N'-ethanesulfonic acid (HEPES), MES). Additionally, salts of the anions (sulfate, citrate, chloride, acetate, phosphate, malonate and tartrate) were preferred for crystallization. Analysis of the protein constructs revealed that MK2 was a 400 amino acid protein consisting of five domains, an N-terminal proline rich domain, a kinase catalytic domain, a C-terminal kinase autoinhibitory domain, nuclear export signal, and a nuclear localization sequence, which also the postulated site for p38 binding.(272 pages)

L15 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2002310533 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12052889
TITLE: Distinct cellular functions of MK2.
AUTHOR: Kotlyarov Alexey; Yannoni Yvonne; Fritz Susann; Laass Kathrin; Telliez Jean-Baptiste; Pitman Deborah; Lin Lih-Ling; Gaestel Matthias
CORPORATE SOURCE: Institute of Biochemistry, Medical School Hannover, Hannover 30625, Germany.
SOURCE: Molecular and cellular biology, (2002 Jul) Vol. 22, No. 13, pp. 4827-35.
Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 11 Jun 2002
Last Updated on STN: 19 Jul 2002
Entered Medline: 18 Jul 2002

AB Mitogen-activated protein kinase (MAPK)-activated protein kinase 2 (MK2) is activated upon stress by p38 MAPK alpha and -beta, which bind to a basic docking motif in the C terminus of MK2 and which subsequently phosphorylate its regulatory sites. As a result of activation MK2 is exported from the nucleus to the cytoplasm and cotransports active p38 MAPK to this compartment. Here we show that the amount of p38 MAPK is significantly reduced in cells and tissues lacking MK2, indicating a stabilizing effect of MK2 for p38.
Using a murine knockout model, we have previously shown that elimination of MK2 leads to a dramatic reduction of tumor necrosis factor (TNF) production in response to lipopolysaccharide. To further elucidate the role of MK2 in p38 MAPK stabilization and in TNF biosynthesis, we analyzed the ability of two MK2 isoforms and several MK2 mutants to restore both p38 MAPK protein levels and TNF biosynthesis in macrophages. We show that MK2 stabilizes p38 MAPK through its C terminus and that MK2 catalytic activity does not contribute to this stabilization. Importantly, we demonstrate that stabilizing p38 MAPK does not restore TNF biosynthesis. TNF biosynthesis is only restored with MK2 catalytic activity. We further show that, in MK2-deficient macrophages, formation of filopodia in response to extracellular stimuli is reduced. In addition, migration of MK2-deficient mouse embryonic fibroblasts (MEFs) and smooth muscle cells on fibronectin is dramatically reduced. Interestingly, reintroducing catalytic MK2 activity into MEFs alone is not sufficient to revert the migratory phenotype of these cells. In addition to catalytic activity, the proline-rich N-terminal region is necessary for rescuing the migratory phenotype. These data indicate that catalytic activity of MK2 is required for both cytokine production and cell migration. However, the proline-rich MK2 N terminus provides a distinct role restricted to cell migration.

L15 ANSWER 3 OF 3 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2002680659 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12440954
TITLE: Is MK2 (mitogen-activated protein kinase-activated protein kinase 2) the key for understanding post-transcriptional regulation of gene expression?.
AUTHOR: Kotlyarov A; Gaestel M
CORPORATE SOURCE: Medical School Hannover, Institute of Biochemistry, Carl-Neuberg-Strasse 1, Germany.
SOURCE: Biochemical Society transactions, (2002 Nov) Vol. 30, No. Pt 6, pp. 959-63. Ref: 46
Journal code: 7506897. ISSN: 0300-5127.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 21 Nov 2002
Last Updated on STN: 11 Jun 2003
Entered Medline: 10 Jun 2003

AB The phenotype of mitogen-activated protein kinase-activated protein kinase-2 (MK2) knockout mice revealed the essential role of this enzyme in post-transcriptional regulation of lipopolysaccharide-induced expression of cytokines such as tumour necrosis factor (TNF)-alpha, interleukin-6 and interferon-gamma, at the level of mRNA stability and translation. In the case of TNF-alpha, this regulation depends on the AU-rich element in TNF-alpha mRNA. In addition to cytokine expression, MK2 is also essential for cell migration in vitro. Although the role of MK2 in cytokine expression depends mainly on catalytic activity, its role in cell migration is also dependent on a proline-rich N-terminal motif. However, the molecular mechanisms involved and the relevant protein targets for MK2 are not completely defined. Here we discuss the possible mechanisms by which two potential target proteins of MK2, small heat-shock protein 25/27 (Hsp25/27) and tristetraprolin, could contribute to our understanding of the above regulation.

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=> d his

     (FILE 'HOME' ENTERED AT 07:41:14 ON 02 AUG 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 07:41:51 ON 02 AUG 2007
L1        12209 S "SHC"
L2        17027 S SH3 (W)DOMAIN
L3          588 S L1 AND L2
L4         2640 S "MAPKAP2 KINASE?" OR "MK2"
L5            0 S L3 AND L4
L6         2372 S MAPKAP####
L7            1 S L3 AND L6
L8            5 S L1 AND L4
L9            2 DUP REM L8 (3 DUPLICATES REMOVED)
L10       12209 S "SHC#"
L11         312 S KINASE(W) BINDING (W)DOMAIN?
L12           6 S L1 AND L11
L13           1 DUP REM L12 (5 DUPLICATES REMOVED)
L14          13 S L4 AND (PROLINE (W)RICH)
L15           3 DUP REM L14 (10 DUPLICATES REMOVED)

=> s l4 (3w)traget?
L16           0 L4 (3W) TRAGET?
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=> s l6 (2w)traget?
L17             0 L6 (2W) TRAGET?

=> s l6 (2w)target?
L18             2 L6 (2W) TARGET?

=> d 1-2 ibib ab

L18  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2004:484689  HCAPLUS
DOCUMENT NUMBER:          141:51851
TITLE:                    Phosphorylation of p38 MAPK and its downstream targets
                          in SARS coronavirus-infected cells
AUTHOR(S):                Mizutani, Tetsuya; Fukushi, Shuetsu; Saijo, Masayuki;
                          Kurane, Ichiro; Morikawa, Shigeru
CORPORATE SOURCE:         Special Pathogens Laboratory, Department of Virology
                          1, National Institute of Infectious Diseases, Gakuen
                          4-7-1, Musashimurayama, Tokyo, 208-0011, Japan
SOURCE:                   Biochemical and Biophysical Research Communications
                          (2004), 319(4), 1228-1234
                          CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER:                Elsevier Science
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Severe acute respiratory syndrome (SARS) has become a global public health
     emergency. Understanding the mol. mechanisms of SARS-induced cytopathic
     effects (CPEs) is a rational approach for the prevention of SARS, and an
     understanding of the cellular stress responses induced by viral infection
     is important for understanding the CPEs. Polyclonal antibodies, which
     recognized nucleocapsid (N) and membrane (M) proteins, detected viral N
     and M proteins in virus-infected Vero E6 cells at least 6 and 12 h
     post-infection (h.p.i.), resp. Furthermore, detection of DNA ladder and
     cleaved caspase-3 in the virus-infected cells at 24 h.p.i. indicated that
     SARS-CoV infection induced apoptotic cell death. Phosphorylation of p38
     MAPK was significantly up-regulated at 18 h.p.i. in SARS-CoV-infected
     cells. The downstream targets of p38 MAPK, MAPKAPK-2, HSP-27, CREB, and
     eIF4E were phosphorylated in virus-infected cells. The p38 MAPK
     inhibitor, SB203580, inhibited effectively phosphorylation of HSP-27,
     CREB, and eIF4E in SARS-CoV-infected cells. However, viral protein
     synthesis was not affected by treatment of SB203580.
REFERENCE COUNT:          33    THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18  ANSWER 2 OF 2  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         1997:564393  HCAPLUS
DOCUMENT NUMBER:          127:243687
TITLE:                    Target proteins of MAP kinases. Transcription factors
                          and MAPKAP kinases
AUTHOR(S):                Fukunaga, Rikiro
CORPORATE SOURCE:         Med. Sch., Oasaka Univ., Suita, 565, Japan
SOURCE:                   Jikken Igaku (1997), 15(14), 1733-1738
                          CODEN: JIIGEF; ISSN: 0288-5514
PUBLISHER:                Yodosha
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 Japanese
AB   A review with 28 refs., on specificity of MAP kinase signaling pathway
     involved in the gene expression in vertebrates, focusing on the MAP
     kinase-targeted transcription factors and MAPKAP (MAP kinase-activated
     protein kinase) kinase family. Possible role of MAPKAP kinase in
     phosphorylation of the CRE-binding protein and IκBα, and phys.
     association of MAP kinase with substrates are discussed.


=> d his
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     (FILE 'HOME' ENTERED AT 07:41:14 ON 02 AUG 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 07:41:51 ON 02 AUG 2007
L1         12209 S "SHC"
L2         17027 S SH3 (W)DOMAIN
L3           588 S L1 AND L2
L4          2640 S "MAPKAP2 KINASE?" OR "MK2"
L5             0 S L3 AND L4
L6          2372 S MAPKAP####
L7             1 S L3 AND L6
L8             5 S L1 AND L4
L9             2 DUP REM L8 (3 DUPLICATES REMOVED)
L10        12209 S "SHC#"
L11          312 S KINASE(W) BINDING (W)DOMAIN?
L12            6 S L1 AND L11
L13            1 DUP REM L12 (5 DUPLICATES REMOVED)
L14           13 S L4 AND (PROLINE (W)RICH)
L15            3 DUP REM L14 (10 DUPLICATES REMOVED)
L16            0 S L4 (3W)TRAGET?
L17            0 S L6 (2W)TRAGET?
L18            2 S L6 (2W)TARGET?

=> s l4 (3w)target?
L19           44 L4 (3W) TARGET?

=> s l19 and l10
L20            0 L19 AND L10

=> dup rem l19
PROCESSING COMPLETED FOR L19
L21            9 DUP REM L19 (35 DUPLICATES REMOVED)

=> d 1-9 ibib ab

L21  ANSWER 1 OF 9     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:    2007112649     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 17312125
TITLE:               Regulation of suppressor of cytokine signaling 3 (SOCS3)
                     mRNA stability by TNF-alpha involves activation of the
                     MKK6/p38MAPK/MK2 cascade.
AUTHOR:              Ehlting Christian; Lai Wi S; Schaper Fred; Brenndorfer
                     Erwin D; Matthes Raphaela-Jessica; Heinrich Peter C; Ludwig
                     Stephan; Blackshear Perry J; Gaestel Matthias; Haussinger
                     Dieter; Bode Johannes G
CORPORATE SOURCE:    Department of Gastroenterology, Hepatology and
                     Infectiology, Heinrich-Heine University, Moorenstrasse 5,
                     Dusseldorf, Germany.
SOURCE:              Journal of immunology (Baltimore, Md. : 1950), (2007 Mar 1)
                     Vol. 178, No. 5, pp. 2813-26.
                     Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
                     (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:            English
FILE SEGMENT:        Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:         200704
ENTRY DATE:          Entered STN: 22 Feb 2007
                     Last Updated on STN: 25 Apr 2007
                     Entered Medline: 24 Apr 2007
AB   The potential of some proinflammatory mediators to inhibit gp130-dependent
     STAT3 activation by enhancing suppressor of cytokine signaling (SOCS) 3
     expression represents an important molecular mechanism admitting the
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modulation of the cellular response toward gp130-mediated signals. Thus, it is necessary to understand the mechanisms involved in the regulation of SOCS3 expression by proinflammatory mediators. In this study, we investigate SOCS3 expression initiated by the proinflammatory cytokine TNF-alpha. In contrast to IL-6, TNF-alpha increases SOCS3 expression by stabilizing SOCS3 mRNA. Activation of the MAPK kinase 6 (MKK6)/p38(MAPK)-cascade is required for TNF-alpha-mediated stabilization of SOCS3 mRNA and results in enhanced SOCS3 protein expression. In fibroblasts or macrophages deficient for MAPK-activated protein kinase 2 (MK2), a downstream target of the MKK6/p38(MAPK) cascade, basal SOCS3-expression is strongly reduced and TNF-alpha-induced SOCS3-mRNA stabilization is impaired, indicating that MK2 is crucial for the control of SOCS3 expression by p38(MAPK)-dependent signals. As a target for SOCS3 mRNA stability-regulating signals, a region containing three copies of a pentameric AUUUA motif in close proximity to a U-rich region located between positions 2422 and 2541 of the 3' untranslated region of SOCS3 is identified. One factor that could target this region is the zinc finger protein tristetraprolin (TTP), which is shown to be capable of destabilizing SOCS3 mRNA via this region. However, data from TTP-deficient cells suggest that TTP does not play an irreplaceable role in the regulation of SOCS3 mRNA stability by TNF-alpha. In summary, these data indicate that TNF-alpha regulates SOCS3 expression on the level of mRNA stability via activation of the MKK6/p38(MAPK) cascade and that the activation of MK2, a downstream target of p38(MAPK), is important for the regulation of SOCS3 expression.

L21 ANSWER 2 OF 9 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2007274239 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17397860
TITLE: Ischemic preconditioning involves dual cardio-protective axes with p38MAPK as upstream target.
AUTHOR: Nagy Norbert; Shiroto Keisuke; Malik Gautam; Huang Chi-Kuang; Gaestel Mathias; Abdellatif Maha; Tosaki Arpad; Maulik Nilanjana; Das Dipak K
CORPORATE SOURCE: FAHA Cardiovascular Research Center, University of Connecticut School of Medicine Farmington, Cardiovascular Research Institute, CT 06030-1110, USA.
CONTRACT NUMBER: HL 22559 (NHLBI)
HL 33889 (NHLBI)
HL 56803 (NHLBI)
SOURCE: Journal of molecular and cellular cardiology, (2007 May) Vol. 42, No. 5, pp. 981-90. Electronic Publication: 2007-02-24.
Journal code: 0262322. ISSN: 0022-2828.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200707
ENTRY DATE: Entered STN: 9 May 2007
Last Updated on STN: 27 Jul 2007
Entered Medline: 26 Jul 2007

AB The existing literature indicates a crucial role of p38 MAP (mitogen-activated protein) kinase (p38MAPK) and its downstream target MAPKAP kinase 2 (MK2) in ischemic preconditioning (IPC). Accordingly, deletion of MK2 gene should abolish the cardioprotective ability of IPC. Interestingly, we were able to partially precondition the hearts from MK2(-/-) knockout mice suggesting the existence of an as yet unknown alternative downstream target of p38MAPK. A recent study from our laboratory also determined a crucial role of CREB (cyclic AMP response element binding protein) in IPC. Since CREB is a downstream target of MSK-1 (mitogen- and stress-activated protein kinase-1) situated at the

crossroad of ERK (extracellular receptor kinase) and p38MAPK signaling pathways, we reasoned that MSK-1 could be a downstream molecular target for p38MAPK and ERK signaling in the IPC hearts. To test this hypothesis, the rat hearts were subjected to IPC by four cyclic episodes of 5 min ischemia and 10 min reperfusion. As expected, IPC induced the activation of ERK1/2, p38MAPK, MK2 and HSP (heat shock protein) 27 as evidenced by their increased phosphorylation; and the inhibition of p38MAPK with SB203580 almost completely, and the inhibition of ERK1/2 with PD098059 partially, abolished cardioprotective effects of IPC. Inhibition of MSK-1 with short hairpin RNA (shRNA) also abolished the IPC-induced cardioprotection. SB203580 partially blocked the effects of MSK-1 suggesting that MSK-1 sits downstream of p38MAPK. shRNA-MSK-1 blocked the contribution of both p38MAPK and ERK1/2 as it is uniquely situated at the downstream crossroad of both of these MAP kinases. Although MSK-1 sits downstream of both ERK1/2 and p38MAPK, ERK1/2 activation appears to play less significant role compared to p38MAPK, since its inhibition blocked MSK activation only partially. Consistent with these results, shRNA-MSK-1 blocked the partial PC in MK2(-/-) hearts, and in combination with SB203580, completely abolished the PC effects in the wild-type hearts. The IPC-induced survival signaling was almost completely inhibited with SB203580, and only partially with PD 098059 as evidenced from the inhibition patterns of IPC induced activation of CREB, Akt and Bcl-2. Again SB203580 alone or in combination with shRNA-MSK-1 inhibited IPC induced survival signal comparatively, suggesting that MSK-1 exists downstream of p38MAPK. Taken together, these results indicate for the first time MSK-1 as an alternative (other than MK2) downstream target for p38MAPK, which also transmits survival signal through the activation of CREB.

L21 ANSWER 3 OF 9 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2006036580 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16424170
TITLE: Protein expression of TNF-alpha in psoriatic skin is regulated at a posttranscriptional level by MAPK-activated protein kinase 2.
AUTHOR: Johansen Claus; Funding Anne Toftegaard; Otkjaer Kristian; Kragballe Knud; Jensen Uffe Birk; Madsen Mogens; Binderup Lise; Skak-Nielsen Tine; Fjording Marianne Scheel; Iversen Lars
CORPORATE SOURCE: Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark.. clausoglotte@hotmail.com
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2006 Feb 1) Vol. 176, No. 3, pp. 1431-8.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 21 Jan 2006
Last Updated on STN: 25 Mar 2006
Entered Medline: 24 Mar 2006

AB Alterations in specific signal transduction pathways may explain the increased expression of proinflammatory cytokines seen in inflammatory diseases such as psoriasis. We reveal increased TNF-alpha protein expression, but similar TNF-alpha mRNA levels, in lesional compared with nonlesional psoriatic skin, demonstrating for the first time that TNF-alpha expression in lesional psoriatic skin is regulated posttranscriptionally. Increased levels of activated MAPK-activated protein kinase 2 (MK2) together with increased MK2 kinase activity were found in lesional compared with nonlesional psoriatic skin. Immunohistochemical analysis showed that activated MK2 was located in the basal layers of the psoriatic epidermis, whereas no positive staining was seen in nonlesional psoriatic skin. In vitro experiments demonstrated

that both anisomycin and IL-1beta caused a significant activation of p38 MAPK and MK2 in cultured normal human keratinocytes. In addition, TNF-alpha protein levels were significantly up-regulated in keratinocytes stimulated with anisomycin or IL-1beta. This increase in TNF-alpha protein expression was completely blocked by the p38 inhibitor, SB202190. Transfection of cultured keratinocytes with MK2-specific small interfering RNA led to a significant decrease in MK2 expression and a subsequent significant reduction in the protein expression of the proinflammatory cytokines TNF-alpha, IL-6, and IL-8, whereas no change in the expression of the anti-inflammatory cytokine IL-10 was seen. This is the first time that MK2 expression and activity have been investigated in an inflammatory disease such as psoriasis. The results strongly suggest that increased activation of MK2 is responsible for the elevated and posttranscriptionally regulated TNF-alpha protein expression in psoriatic skin, making MK2 a potential target in the treatment of psoriasis.

L21 ANSWER 4 OF 9 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2005064150 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15692053
TITLE: The kaposin B protein of KSHV activates the p38/MK2 pathway and stabilizes cytokine mRNAs.
AUTHOR: McCormick Craig; Ganem Don
CORPORATE SOURCE: Howard Hughes Medical Institute, Department of Microbiology and Immunology, and Department of Medicine, University of California, San Francisco, CA 94143, USA.
SOURCE: Science (New York, N.Y.), (2005 Feb 4) Vol. 307, No. 5710, pp. 739-41.
Journal code: 0404511. E-ISSN: 1095-9203.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200502
ENTRY DATE: Entered STN: 5 Feb 2005
Last Updated on STN: 17 Feb 2005
Entered Medline: 16 Feb 2005

AB Cytokine production plays a critical role in diseases caused by Kaposi's sarcoma-associated herpesvirus (KSHV). Here we show that a latent KSHV gene product, kaposin B, increases the expression of cytokines by blocking the degradation of their messenger RNAs (mRNAs). Cytokine transcripts are normally unstable because they contain AU-rich elements (AREs) in their 3' noncoding regions that target them for degradation. Kaposin B reverses this instability by binding to and activating the kinase MK2, a target of the p38 mitogen-activated protein kinase signaling pathway and a known inhibitor of ARE-mRNA decay. These findings define an important mechanism linking latent KSHV infection to cytokine production, and also illustrate a distinctive mode by which viruses can selectively modulate mRNA turnover.

L21 ANSWER 5 OF 9 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2005:523934 BIOSIS
DOCUMENT NUMBER: PREV200510313897
TITLE: MAPKAPK-2 and serine phospharylation of HSP25/27 and alpha B-crystallin do not increase myocardial resistance to infarction.
AUTHOR(S): Gorog, Diana A. [Reprint Author]; Tanno, Masaya; Fisher, Simon; Bin Cao, Xuo; Bellahcene, Mohamed; Kabir, Alamgir M.; Quinlan, Roy A.; Kato, Kanefusa; Marber, Michael S.
CORPORATE SOURCE: St Thomas Hosp, London, UK
SOURCE: Circulation, (OCT 26 2004) Vol. 110, No. 17, Suppl. S, pp. 67.
Meeting Info.: 77th Scientific Meeting of the American-Heart-Association. New Orleans, LA, USA. November

07 -10, 2004. Amer Heart Assoc.
CODEN: CIRCAZ. ISSN: 0009-7322.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Dec 2005
Last Updated on STN: 1 Dec 2005

AB MAPKAPK-2 and the phosphorylation of its downstream targets HSP25/27 (pHSP25/27) and alpha B-crystallin (p alpha BC) are thought to contribute to ischemic preconditioning (IP) and increased resistance to myocardial ischemia. We examined this contribution by using MAFKAPK-2 deficient mice. Using wild-type (MK2(-/-)) and knock-out (MK2(-/-)) mice with targeted disruption of both MAPKAPK-2 alleles, we compared infarct size:area at risk volume ratios (IS:AAR%) in Langendorff-perfused hearts after 30 min global ischemia and 2 h reperfusion following pre-treatment with the p38 MAPK-inhibitor SB203580 (1 mu mol/L in 0.01 % DMSO) or vehicle (0.01% DMSO). The sensitivity to IP was assessed with 4 cycles of ischemia/reperfusion prior to the 30 min ischemia. IS:AAR% in MK2(+/+) and MK2(-/-) hearts were similar (65.8 +/- 4 v,; 70 +/- 5, p=0.9). IS:AAR% were reduced by SB203580 in both MK2(+/+) (52.7 +/- 3) and MK2(-/-) (52 +/- 5) hearts (Fig.1A); and were also reduced by IP, in MK2(+/+) (26.5 +/- 4) and MK2-1- hearts (28.6 +/- 3) (Fig.1B). Ischemia- and IP-induced p38 MAPK phosphorylation was accompanied by the phosphorylation of HSP25/27 in MK2(+/+) but not in MK2(-/-) hearts (Fig.1C and D). The phosphorylation of alpha BC was more complex, though temporally related to p38-MAPK activation, it was only partially prevented by SB203580 or the absence of MK2, suggesting alternate pathway(s) of phosphorylation. In conclusion, the absence of MK2 and HSP25/27 phosphorylation during ischemia and IP does not affect myocardial sensitivity to ischemia. Intra-ischemic activation of p38 MAPK has a detrimental effect on infarct size that is independent of MK2 and pHSP25/27, and is likely mediated through alternative substrates.[GRAPHICS]rms of proximal signalling components (gap junctions and PKC), but share common distal mediators (PI3-kinase and mitochondrial K-ATP channels).[GRAPHICS]eam Akt-FKHR signaling pathways, resulting in actin cleavage, increased expression of ubiquitin ligases, and increased ubiquitinization and proteolysis via the ubiquitin-proteasome pathway. Our findings have major indications for understanding mechanisms of skeletal muscle atropy in CHF.

L21 ANSWER 6 OF 9 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2002096858 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11741878
TITLE: MK2 targets AU-rich elements and regulates biosynthesis of tumor necrosis factor and interleukin-6 independently at different post-transcriptional levels.
AUTHOR: Neininger Armin; Kontoyiannis Dimitris; Kotlyarov Alexey; Winzen Reinhard; Eckert Rolf; Volk Hans-Dieter; Holtmann Helmut; Kollias George; Gaestel Matthias
CORPORATE SOURCE: Innovationskolleg Zellspezialisierung, Martin-Luther-Universitat Halle/Wittenberg, 06120 Halle, Germany.
SOURCE: The Journal of biological chemistry, (2002 Feb 1) Vol. 277, No. 5, pp. 3065-8. Electronic Publication: 2001-12-06.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 6 Feb 2002
Last Updated on STN: 5 Jan 2003
Entered Medline: 28 Feb 2002

AB We demonstrate that lipopolysaccharide-induced tumor necrosis factor (TNF) biosynthesis becomes independent of MAPKAP kinase 2 (MK2) when the AU-rich element (ARE) of the TNF gene is deleted. In spleen cells and macrophages where TNF biosynthesis is restored as a result of this deletion, interleukin (IL)-6 biosynthesis is still dependent on MK2. In MK2-deficient macrophages the half-life of IL-6 mRNA is reduced more than 10-fold, whereas the half-life of TNF mRNA is only weakly decreased. It is shown that the stability of a reporter mRNA carrying the AU-rich 3'-untranslated region (3'-UTR) of IL-6 is increased by MK2. The data provide in vivo evidence that the AU-rich 3'-UTRs of TNF and IL-6 are downstream to MK2 signaling and make MK2 an essential component of mechanisms that regulate biosynthesis of IL-6 at the levels of mRNA stability, and of TNF mainly through TNF-ARE-dependent translational control.

L21 ANSWER 7 OF 9 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001216883 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11250897
TITLE: Adenovirus-activated PKA and p38/MAPK pathways boost microtubule-mediated nuclear targeting of virus.
AUTHOR: Suomalainen M; Nakano M Y; Boucke K; Keller S; Greber U F
CORPORATE SOURCE: University of Zurich, Institute of Zoology, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland.
SOURCE: The EMBO journal, (2001 Mar 15) Vol. 20, No. 6, pp. 1310-9. Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 25 Apr 2001
Last Updated on STN: 20 Apr 2002
Entered Medline: 19 Apr 2001

AB Nuclear targeting of adenovirus is mediated by the microtubule-dependent, minus-end-directed motor complex dynein/dynactin, in competition with plus- end-directed motility. We demonstrate that adenovirus transiently activates two distinct signaling pathways to enhance nuclear targeting. The first pathway activates integrins and cAMP-dependent protein kinase A (PKA). The second pathway activates the p38/MAP kinase and the downstream MAPKAP kinase 2 (MK2), dependent on the p38/MAPK kinase MKK6, but independent of integrins and PKA. Motility measurements in PKA-inhibited, p38-inhibited or MK2-lacking (MK2(-/-)) cells indicate that PKA and p38 stimulated both the frequency and velocity of minus-end-directed viral motility without affecting the perinuclear localization of transferrin-containing endosomal vesicles. p38 also suppressed lateral viral motilities and MK2 boosted the frequency of minus-end-directed virus transport. Nuclear targeting of adenovirus was rescued in MK2(-/-) cells by overexpression of hsp27, an MK2 target that enhances actin metabolism. Our results demonstrate that complementary activities of PKA, p38 and MK2 tip the transport balance of adenovirus towards the nucleus and thus enhance infection.

L21 ANSWER 8 OF 9 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1999244903 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10228013
TITLE: The role of p38 mitogen-activated protein kinase in IL-1 beta transcription.
AUTHOR: Baldassare J J; Bi Y; Bellone C J
CORPORATE SOURCE: Department of Pharmacological and Physiological Sciences, St. Louis University School of Medicine, St. Louis, MO 63104, USA.
CONTRACT NUMBER: HL 40901 (NHLBI)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1999 May 1)

Vol. 162, No. 9, pp. 5367-73.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 1 Jun 1999
Last Updated on STN: 1 Jun 1999
Entered Medline: 20 May 1999

AB Several reports have shown that bicyclic imidazoles, specific inhibitors of the p38 mitogen-activated protein kinase (MAPK), block cytokine synthesis at the translational level. In this study, we examined the role of p38 MAPK in the regulation of the IL-1beta cytokine gene in monocytic cell lines using the bicyclic imidazole SB203580. Addition of SB203580 30 min before stimulation of monocytes with LPS inhibited IL-1beta protein and steady state message in a dose-dependent manner in both RAW264.7 and J774 cell lines. The loss of IL-1beta message was due mainly to inhibition of transcription, since nuclear run-off analysis showed an approximately 80% decrease in specific IL-1 RNA synthesis. In contrast, SB203580 had no effect on the synthesis of TNF-alpha message. LPS-stimulated p38 MAPK activity in the RAW264.7 cells was blocked by SB203580, as measured by the inhibition of MAPKAP2 kinase activity, a downstream target of the p38 MAPK. CCAATT/enhancer binding protein (C/EBP)/NFIL-6-driven chloramphenicol acetyltransferase (CAT) reporter activity was sensitive to SB203580, indicating that C/EBP/NFIL-6 transcription factor(s) are also targets of p38 MAPK. In contrast, transfected CAT constructs containing NF-kappaB elements were only partially inhibited (approximately 35%) at the highest concentration of SB203580 after LPS stimulation. As measured by EMSA, LPS-stimulated NF-kappaB activation was not affected by SB203580. Overall, the results demonstrate, for the first time, a role for p38 MAPK in IL-1beta transcription by acting through C/EBP/NFIL-6 transcription factors.

L21 ANSWER 9 OF 9 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1999417578 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10487749
TITLE: The p38 MAP kinase pathway signals for cytokine-induced mRNA stabilization via MAP kinase-activated protein kinase 2 and an AU-rich region-targeted mechanism.
AUTHOR: Winzen R; Kracht M; Ritter B; Wilhelm A; Chen C Y; Shyu A B; Muller M; Gaestel M; Resch K; Holtmann H
CORPORATE SOURCE: Institute of Molecular Pharmacology, Medical School Hannover, D-30623 Hannover, Germany.
SOURCE: The EMBO journal, (1999 Sep 15) Vol. 18, No. 18, pp. 4969-80.
Journal code: 8208664. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 11 Jan 2000
Last Updated on STN: 20 Apr 2002
Entered Medline: 4 Nov 1999

AB Stabilization of mRNAs contributes to the strong and rapid induction of genes in the inflammatory response. The signaling mechanisms involved were investigated using a tetracycline-controlled expression system to determine the half-lives of interleukin (IL)-6 and IL-8 mRNAs. Transcript stability was low in untreated HeLa cells, but increased in cells

expressing a constitutively active form of the MAP kinase kinase kinase MEKK1. Destabilization and signal-induced stabilization was transferred to the stable beta-globin mRNA by a 161-nucleotide fragment of IL-8 mRNA which contains an AU-rich region, as well as by defined AU-rich elements (AREs) of the c-fos and GM-CSF mRNAs. Of the different MEKK1-activated signaling pathways, no significant effects on mRNA degradation were observed for the SAPK/JNK, extracellular regulated kinase and NF-kappaB pathways. Selective activation of the p38 MAP kinase (=SAPK2) pathway by MAP kinase kinase 6 induced mRNA stabilization. A dominant-negative mutant of p38 MAP kinase interfered with MEKK1 and also IL-1-induced stabilization. Furthermore, an active form of the p38 MAP kinase-activated protein kinase (MAPKAP K2 or MK2) induced mRNA stabilization, whereas a negative interfering MK2 mutant interfered with MAP kinase kinase 6-induced stabilization. These findings indicate that the p38 MAP kinase pathway contributes to cytokine/stress-induced gene expression by stabilizing mRNAs through an MK2-dependent, ARE-targeted mechanism.

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=> d his

     (FILE 'HOME' ENTERED AT 07:41:14 ON 02 AUG 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS,
     LIFESCI' ENTERED AT 07:41:51 ON 02 AUG 2007
L1        12209 S "SHC"
L2        17027 S SH3 (W)DOMAIN
L3          588 S L1 AND L2
L4         2640 S "MAPKAP2 KINASE?" OR "MK2"
L5            0 S L3 AND L4
L6         2372 S MAPKAP####
L7            1 S L3 AND L6
L8            5 S L1 AND L4
L9            2 DUP REM L8 (3 DUPLICATES REMOVED)
L10       12209 S "SHC#"
L11         312 S KINASE(W) BINDING (W)DOMAIN?
L12           6 S L1 AND L11
L13           1 DUP REM L12 (5 DUPLICATES REMOVED)
L14          13 S L4 AND (PROLINE (W)RICH)
L15           3 DUP REM L14 (10 DUPLICATES REMOVED)
L16           0 S L4 (3W)TRAGET?
L17           0 S L6 (2W)TRAGET?
L18           2 S L6 (2W)TARGET?
L19          44 S L4 (3W)TARGET?
L20           0 S L19 AND L10
L21           9 DUP REM L19 (35 DUPLICATES REMOVED)

=> d l9 1-2 ibib ab

L9    ANSWER 1 OF 2  BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
      DUPLICATE 1
ACCESSION NUMBER: 2004-09118  BIOTECHDS
TITLE:            New isolated, purified or recombinant protein complex
                  comprising an MK2 polypeptide, and an MK2
                  interacting protein chosen from STS, HPH2 and Shc
                  for treating or preventing e.g. Crohn's disease, or
                  rheumatoid arthritis;
                     involving vector-mediated gene transfer and expression in
                     host cell for use in gene therapy
AUTHOR:           LIN L; YANNONI Y M
PATENT ASSIGNEE:  WYETH
PATENT INFO:      WO 2004012660 12 Feb 2004
APPLICATION INFO: WO 2003-US23981 1 Aug 2003
PRIORITY INFO:    US 2002-400044 2 Aug 2002; US 2002-400044 2 Aug 2002
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DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2004-156998 [15]

AB DERWENT ABSTRACT:

NOVELTY - An isolated, purified or recombinant protein complex comprising a mitogen-activated protein kinase-activated protein kinase 2 (MK2) polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a host cell comprising a first and a second nucleic acid, where the first nucleic acid encodes a recombinant MK2 polypeptide and the second nucleic acid encoding MK2 interacting protein; (2) an assay for determining whether the test compound inhibits or promotes formation of a protein complex; (3) a method for determining whether a test compound affects MK2 activity; (4) an screening assay to identify compounds that inhibit or promote formation of the protein complex; (5) an antibody that binds one or more proteins in the complex; (6) a method for modulating formation of a protein complex in a cell comprising at least a first and a second protein; (7) a method for producing a complex; (8) a drug screening method for identifying anti-inflammatory drugs; (9) a method of modulating inflammation in a tissue; (10) a method of treating or preventing inflammation in a tissue; (11) a method of treating a patient suffering from at least one inflammatory condition; (12) a method of expressing a nucleic acid in a cell to inhibit inflammation; (13) a method of detecting at least one of the absence, presence and amount of MK2 in a sample; (14) a kit that enables qualitative detection of MK2 comprising a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and at least one other kit component chosen from: at least one of buffer and solution; and at least one structural component; and (15) a pharmaceutical composition comprising at least one protein that binds MK2, and at least one carrier.

BIOTECHNOLOGY - Preferred Complex: The protein complex comprises an MK2 polypeptide and at least one or two MK2 interacting protein. The MK2 interacting protein is chosen from STS, HPH2 and Shc. The MK2 polypeptide comprises a fusion protein. The fusion protein comprises a domain for purifying, isolating or detecting the fusion protein. The fusion protein comprises a domain chosen from affinity tags, radionucleotides, enzymes, and fluorophores. The domain is selected from polyhistidine, FLAG, Glu-Glu, glutathione S transferase (GST), thioredoxin, protein A, protein G, and an immunoglobulin heavy chain constant region. Preferred Method: Determining whether a test compound inhibits or promotes formation of a protein complex comprises forming a reaction mixture including an MK2 polypeptide, at least one MK2 interacting protein and the test compound; and detecting the presence of the protein complex between MK2 and the MK2 interacting protein, where a difference in the amount of complex in the presence of the test compound, relative to the amount of complex in the absence of the test compound indicates that the test compound inhibits or promotes complex formation. An increase in the amount of complex in presence of the test compound indicates that the test compound promotes complex formation. A decrease in the amount of complex in presence of the test compound indicates that the test compound inhibits complex formation. Determining whether a test compound affects MK2 activity comprises forming a protein complex comprising an MK2 polypeptide and an MK2 interacting protein; contacting the protein complex with the test compound; and determining the effect of the test compound on one or more activities chosen from MK2 kinase activity, an amount of MK2 in the complex, production of TNF, and amount of phosphorylated form of a substrate of MK2. The screening assay to identify compounds that inhibit or promote formation of a protein

complex, comprises providing a two-hybrid assay system including a first fusion protein comprising an MK2 polypeptide, and a second fusion protein comprising a polypeptide chosen from one or more of STS, HPH2 and Shc, under conditions where the two proteins interact in the two hybrid assay system; measuring a level of interaction between the fusion proteins in the presence and in the absence of a test compound; and comparing the level of interaction of the fusion proteins, where a decrease in the level of interaction is indicative of a compound that inhibits the interaction between the MK2 polypeptide and a polypeptide chosen from one or more of STS, HPH2 and Shc. Modulating formation of a protein complex in a cell comprising at least a first protein and a second protein, where the first protein is an MK2 polypeptide and the second protein is chosen from one or more of STS, HPH2 and Shc, comprises administering to the cell a compound capable of modulating formation of the complex. Producing a complex comprises transfecting a cell with one or more polynucleotides encoding an MK2 polypeptide and an MK2 interacting protein chosen from one or more of STS and Shc, where the polypeptides form a complex. The drug screening method for identifying anti-inflammatory drugs comprises providing MK2 and at least one MK2-interacting protein; allowing MK2 and the protein to interact to form a complex; adding an effective amount of a potential drug to the complex; and determining whether the potential drug inhibits complex formation. The MK2 and the protein interact in vivo in a yeast or mammalian 2-hybrid system. The MK2 and the protein interact in vitro. The protein is STS, Shc or HPH2. The drug is a small molecule, peptide or protein, antibody, or chemical agent. Modulating inflammation in a tissue comprises administering a nucleic acid that encodes an MK2 interacting protein to the tissue; and allowing the nucleic acid to express the MK2 interacting protein, thus to modulate inflammation in the tissue. The nucleic acid expresses a protein chosen from STS, HPH2 and Shc. Treating or preventing inflammation in a tissue comprises administering to the tissue a therapeutically effective amount of at least one agent that blocks the interaction between MK2 and an MK2 interacting protein; or allows the interaction, but blocks MK2 activity. The agent is an antibody, preferably a polyclonal or monoclonal antibody. The antibody binds MK2 or the MK2 -interacting protein. The agent is a chemical agent, a peptide or protein, or a small molecule. Modulating inflammation in a tissue comprises contacting the tissue with at least one protein that binds MK2; and allowing the protein to modulate inflammation in the tissue. Treating a patient suffering from at least one inflammatory condition, comprises administering a therapeutically effective dose of at least one compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the compound to bind to at least one of MK2 or an MK2 complex and modulate inflammation. The protein or peptide is a mutant form of a wild-type protein or peptide, which stimulates MK2 activity. Expressing a nucleic acid in a cell to inhibit inflammation comprises adding at least one nucleic acid encoding a compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the cell to express the compound and inhibit inflammation. Detecting at least one of the absence, presence, and amount of MK2 in a sample, comprises administering at least one compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and correlating the absence, presence, or amount of bound protein or compound with the absence, presence, or amount of MK2 in the sample. Preferred Antibody: The antibody inhibits interaction of MK2

with the MK2 interacting protein. Preferred Kit: The kit further comprises an agent that binds the protein or compound. The agent is an antibody.

ACTIVITY - Antiinflammatory; Gastrointestinal; Antiarthritic; Antirheumatic; Respiratory-Gen; Antiasthmatic; Immunosuppressive; Antiulcer. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The composition and methods are useful for treating or preventing a condition chosen from Crohn's disease, inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, acute respiratory distress syndrome, emphysema, delayed type hypersensitivity reaction, asthma, systemic lupus erythematosus, and inflammation due to trauma or injury (claimed).

ADMINISTRATION - Dosage is 5-500, preferably 40-60 mg per kg. Administration is intravenous, intramuscular, rectal or subcutaneous.

EXAMPLE - Experimental protocols are described but no results are given. (107 pages)

L9 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2004196650 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15094067
TITLE: P66(ShcA) interacts with MAPKAP kinase 2 and regulates its activity.
AUTHOR: Yannoni Yvonne M; Gaestel Matthias; Lin Lih-Ling
CORPORATE SOURCE: Department of Inflammation, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140-2311, USA.. yvonne.yannoni@abbott.com
SOURCE: FEBS letters, (2004 Apr 23) Vol. 564, No. 1-2, pp. 205-11. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20 Apr 2004
Last Updated on STN: 4 Jun 2004
Entered Medline: 3 Jun 2004

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66(ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation.

=> d his

(FILE 'HOME' ENTERED AT 07:41:14 ON 02 AUG 2007)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 07:41:51 ON 02 AUG 2007

L1 12209 S "SHC"
L2 17027 S SH3 (W)DOMAIN
L3 588 S L1 AND L2
L4 2640 S "MAPKAP2 KINASE?" OR "MK2"
L5 0 S L3 AND L4
L6 2372 S MAPKAP####
L7 1 S L3 AND L6
L8 5 S L1 AND L4

```
L9            2 DUP REM L8 (3 DUPLICATES REMOVED)
L10       12209 S "SHC#"
L11         312 S KINASE(W) BINDING (W)DOMAIN?
L12           6 S L1 AND L11
L13           1 DUP REM L12 (5 DUPLICATES REMOVED)
L14          13 S L4 AND (PROLINE (W)RICH)
L15           3 DUP REM L14 (10 DUPLICATES REMOVED)
L16           0 S L4 (3W)TRAGET?
L17           0 S L6 (2W)TRAGET?
L18           2 S L6 (2W)TARGET?
L19          44 S L4 (3W)TARGET?
L20           0 S L19 AND L10
L21           9 DUP REM L19 (35 DUPLICATES REMOVED)

=> s l4 and "66K##"
L22           0 L4 AND "66K##"

=> s l10 and (l6 or l4)
L23          13 L10 AND (L6 OR L4)

=> dup rem l23
PROCESSING COMPLETED FOR L23
L24          10 DUP REM L23 (3 DUPLICATES REMOVED)

=> d 1-10 ibib ab

L24  ANSWER 1 OF 10  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2005:121193  HCAPLUS
DOCUMENT NUMBER:          142:214836
TITLE:                    Biomarkers of cyclin-dependent kinase modulation in
                          cancer therapy
INVENTOR(S):              Li, Martha; Rupnow, Brent A.; Webster, Kevin R.;
                          Jackson, Donald G.; Wong, Tai W.
PATENT ASSIGNEE(S):       Bristol-Myers Squibb Company, USA
SOURCE:                   PCT Int. Appl., 141 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2005012875         A2    20050210    WO 2004-US24424         20040729
     WO 2005012875         A3    20070315
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG
     AU 2004262369         A1    20050210    AU 2004-262369          20040729
     CA 2533803            A1    20050210    CA 2004-2533803         20040729
     EP 1656542            A2    20060517    EP 2004-779471          20040729
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR
     JP 2007507204         T     20070329    JP 2006-522045          20040729
     US 2007105114         A1    20070510    US 2006-567867          20060818
PRIORITY APPLN. INFO.:                       US 2003-490890P      P  20030729
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WO 2004-US24424 W 20040729

AB Biomarkers having expression patterns that correlate with a response of cells to treatment with one or more cdk modulating agents, and uses thereof. Transcription profiling was used to identify the biomarkers. Specifically, transcription profiling of the effect of a certain cdk2 inhibitor (BMS 387032 0.5 L-tartaric acid salt) on peripheral blood mononuclear cells was first performed. Gene chips were used to quantitate the levels of gene expression on a large-scale with Affymetrix human gene chips HG-U95A, B, and C. Next, profiling of a cdk2 inhibitor-treated tumor cell line A28780 at multiple doses and time points was performed to establish a correlation of tumor site response with peripheral blood biomarkers. In order to establish the mol. target-specificity of the potential biomarkers, tumor cell line A2780 treated with anti-cdk2 oligonucleotides was also profiles. Overlapping gene expression changes were selected for further evaluation in human ovarian carcinoma xenograft A2780 that were treated with the cdk2 inhibitor. The selected biomarkers were subjected to real-time PCR anal. in order to verify the observed changes from the gene chip anal. The biomarker comprising GenBank accession number W28729 was discovered to have the most consistent and robust regulation in response to cdk inhibition. Provided are methods for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer that comprises administering an agent that modulates cdk activity.

L24 ANSWER 2 OF 10 BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
DUPLICATE 1

ACCESSION NUMBER: 2004-09118 BIOTECHDS

TITLE: New isolated, purified or recombinant protein complex comprising an MK2 polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc for treating or preventing e.g. Crohn's disease, or rheumatoid arthritis;
involving vector-mediated gene transfer and expression in host cell for use in gene therapy

AUTHOR: LIN L; YANNONI Y M

PATENT ASSIGNEE: WYETH

PATENT INFO: WO 2004012660 12 Feb 2004

APPLICATION INFO: WO 2003-US23981 1 Aug 2003

PRIORITY INFO: US 2002-400044 2 Aug 2002; US 2002-400044 2 Aug 2002

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: WPI: 2004-156998 [15]

AB DERWENT ABSTRACT:

NOVELTY - An isolated, purified or recombinant protein complex comprising a mitogen-activated protein kinase-activated protein kinase 2 (MK2) polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a host cell comprising a first and a second nucleic acid, where the first nucleic acid encodes a recombinant MK2 polypeptide and the second nucleic acid encoding MK2 interacting protein; (2) an assay for determining whether the test compound inhibits or promotes formation of a protein complex; (3) a method for determining whether a test compound affects MK2 activity; (4) an screening assay to identify compounds that inhibit or promote formation of the protein complex; (5) an antibody that binds one or more proteins in the complex; (6) a method for modulating formation of a protein complex in a cell comprising at least a first and a second protein; (7) a method for producing a complex; (8) a drug screening method for identifying anti-inflammatory drugs; (9) a method of modulating inflammation in a tissue; (10) a method of treating or preventing inflammation in a tissue; (11) a method of treating a patient suffering from at least one inflammatory condition; (12) a method of expressing a nucleic acid in a cell to inhibit inflammation; (13) a

method of detecting at least one of the absence, presence and amount of MK2 in a sample; (14) a kit that enables qualitative detection of MK2 comprising a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and at least one other kit component chosen from: at least one of buffer and solution; and at least one structural component; and (15) a pharmaceutical composition comprising at least one protein that binds MK2, and at least one carrier.

BIOTECHNOLOGY - Preferred Complex: The protein complex comprises an MK2 polypeptide and at least one or two MK2 interacting protein. The MK2 interacting protein is chosen from STS, HPH2 and Shc. The MK2 polypeptide comprises a fusion protein. The fusion protein comprises a domain for purifying, isolating or detecting the fusion protein. The fusion protein comprises a domain chosen from affinity tags, radionucleotides, enzymes, and fluorophores. The domain is selected from polyhistidine, FLAG, Glu-Glu, glutathione S transferase (GST), thioredoxin, protein A, protein G, and an immunoglobulin heavy chain constant region. Preferred Method: Determining whether a test compound inhibits or promotes formation of a protein complex comprises forming a reaction mixture including an MK2 polypeptide, at least one MK2 interacting protein and the test compound; and detecting the presence of the protein complex between MK2 and the MK2 interacting protein, where a difference in the amount of complex in the presence of the test compound, relative to the amount of complex in the absence of the test compound indicates that the test compound inhibits or promotes complex formation. An increase in the amount of complex in presence of the test compound indicates that the test compound promotes complex formation. A decrease in the amount of complex in presence of the test compound indicates that the test compound inhibits complex formation. Determining whether a test compound affects MK2 activity comprises forming a protein complex comprising an MK2 polypeptide and an MK2 interacting protein; contacting the protein complex with the test compound; and determining the effect of the test compound on one or more activities chosen from MK2 kinase activity, an amount of MK2 in the complex, production of TNF, and amount of phosphorylated form of a substrate of MK2. The screening assay to identify compounds that inhibit or promote formation of a protein complex, comprises providing a two-hybrid assay system including a first fusion protein comprising an MK2 polypeptide, and a second fusion protein comprising a polypeptide chosen from one or more of STS, HPH2 and Shc, under conditions where the two proteins interact in the two hybrid assay system; measuring a level of interaction between the fusion proteins in the presence and in the absence of a test compound; and comparing the level of interaction of the fusion proteins, where a decrease in the level of interaction is indicative of a compound that inhibits the interaction between the MK2 polypeptide and a polypeptide chosen from one or more of STS, HPH2 and Shc. Modulating formation of a protein complex in a cell comprising at least a first protein and a second protein, where the first protein is an MK2 polypeptide and the second protein is chosen from one or more of STS, HPH2 and Shc, comprises administering to the cell a compound capable of modulating formation of the complex. Producing a complex comprises transfecting a cell with one or more polynucleotides encoding an MK2 polypeptide and an MK2 interacting protein chosen from one or more of STS and Shc, where the polypeptides form a complex. The drug screening method for identifying anti-inflammatory drugs comprises providing MK2 and at least one MK2-interacting protein; allowing MK2 and the protein to interact to form a complex; adding an effective amount of a potential drug to the complex; and determining whether the potential drug inhibits complex formation. The MK2 and the protein interact in vivo in a yeast or mammalian 2-hybrid system. The MK2 and the

protein interact in vitro. The protein is STS, Shc or HPH2. The drug is a small molecule, peptide or protein, antibody, or chemical agent. Modulating inflammation in a tissue comprises administering a nucleic acid that encodes an MK2 interacting protein to the tissue; and allowing the nucleic acid to express the MK2 interacting protein, thus to modulate inflammation in the tissue. The nucleic acid expresses a protein chosen from STS, HPH2 and Shc. Treating or preventing inflammation in a tissue comprises administering to the tissue a therapeutically effective amount of at least one agent that blocks the interaction between MK2 and an MK2 interacting protein; or allows the interaction, but blocks MK2 activity. The agent is an antibody, preferably a polyclonal or monoclonal antibody. The antibody binds MK2 or the MK2 -interacting protein. The agent is a chemical agent, a peptide or protein, or a small molecule. Modulating inflammation in a tissue comprises contacting the tissue with at least one protein that binds MK2; and allowing the protein to modulate inflammation in the tissue. Treating a patient suffering from at least one inflammatory condition, comprises administering a therapeutically effective dose of at least one compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the compound to bind to at least one of MK2 or an MK2 complex and modulate inflammation. The protein or peptide is a mutant form of a wild-type protein or peptide, which stimulates MK2 activity. Expressing a nucleic acid in a cell to inhibit inflammation comprises adding at least one nucleic acid encoding a compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the cell to express the compound and inhibit inflammation. Detecting at least one of the absence, presence, and amount of MK2 in a sample, comprises administering at least one compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and correlating the absence, presence, or amount of bound protein or compound with the absence, presence, or amount of MK2 in the sample. Preferred Antibody: The antibody inhibits interaction of MK2 with the MK2 interacting protein. Preferred Kit: The kit further comprises an agent that binds the protein or compound. The agent is an antibody.

ACTIVITY - Antiinflammatory; Gastrointestinal; Antiarthritic; Antirheumatic; Respiratory-Gen; Antiasthmatic; Immunosuppressive; Antiulcer. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The composition and methods are useful for treating or preventing a condition chosen from Crohn's disease, inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, acute respiratory distress syndrome, emphysema, delayed type hypersensitivity reaction, asthma, systemic lupus erythematosus, and inflammation due to trauma or injury (claimed).

ADMINISTRATION - Dosage is 5-500, preferably 40-60 mg per kg. Administration is intravenous, intramuscular, rectal or subcutaneous.

EXAMPLE - Experimental protocols are described but no results are given. (107 pages)

L24 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2004:371064 HCAPLUS
DOCUMENT NUMBER:	140:373461
TITLE:	Evaluation of breast cancer states and outcomes using gene expression profiles
INVENTOR(S):	West, Mike; Nevins, Joseph R.; Huang, Andrew
PATENT ASSIGNEE(S):	Synpac, Inc., USA; Duke University

SOURCE: PCT Int. Appl., 799 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037996	A2	20040506	WO 2003-US33656	20031024
WO 2004037996	A3	20041229		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004083084	A1	20040429	US 2002-291878	20021112
WO 2004044839	A2	20040527	WO 2002-US38216	20021112
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004106113	A1	20040603	US 2002-291886	20021112
AU 2003284880	A1	20040513	AU 2003-284880	20031024

PRIORITY APPLN. INFO.:		
US 2002-420729P	P	20021024
US 2002-421062P	P	20021025
US 2002-421102P	P	20021025
US 2002-424701P	P	20021108
US 2002-424715P	P	20021108
US 2002-424718P	P	20021108
US 2002-291878	A	20021112
US 2002-291886	A	20021112
US 2002-425256P	P	20021112
WO 2002-US38216	A	20021112
WO 2002-US38222	A	20021112
US 2003-448461P	P	20030221
US 2003-448462P	P	20030221
US 2003-457877P	P	20030327
US 2003-458373P	P	20030331
WO 2003-US33656	W	20031024

AB The present invention relates generally to a method for evaluating and/or predicting breast cancer states and outcomes by measuring gene and metagene expression levels and integrating such data with clin. risk factors. Genes and metagenes whose expressions are correlated with a particular breast cancer risk factor or phenotype are provided using binary prediction tree modeling. The invention provides 175 genes associated with metagene predictors of lymph node metastasis, 216 genes associated with metagene predictors of breast cancer recurrence, and 496 metagenes related to breast cancer study. Methods of using the subject genes and metagenes in diagnosis and treatment methods, as well as drug screening methods, etc are also provided. In addition, reagents, media and kits that find use in practicing the subject methods are also provided.

L24 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:533778 HCAPLUS
DOCUMENT NUMBER: 141:65087
TITLE: Gene expression-based method for distinguishing metastatic from non-metastatic forms of a tumor, and use in designing therapeutic drugs
INVENTOR(S): Stephan, Dietrich A.; MacDonald, Tobey J.; Brown, Kevin M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 17 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004126755	A1	20040701	US 2001-940454	20010829
PRIORITY APPLN. INFO.:			US 2001-940454	20010829

AB Gene expression profiling of tumors, clin. designated as either metastatic (M+) or non-metastatic (M0), identifies genes whose expression differed significantly between classes. A class-prediction algorithm based on these medulloblastoma genes assigned the sample class to these tumors (M+ or M0) with 72% accuracy and to four addnl. independent tumors with a 100% accuracy. Class prediction also assigned the metastatic medulloblastoma cell line Daoy to the metastatic class. Notably upregulated in the M+ tumors were platelet derived growth factor receptor alpha (PDGFRA) and members of the downstream RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway. Immunohistochem. validation on an independent set of tumors showed significant overexpression of PDGFRA in M+ tumors as compared to M0 tumors. In in vitro assays, PDGFA enhanced medulloblastoma migration and increased downstream MAP2K1 (MEK1), MAP2K2 (MEK2), MAPK1 (p42 MAPK), and MAPK3 (p44 MAPK) phosphorylation in a dose-dependent manner. Neutralizing antibodies to PDGFRA or U0126, a highly specific chemical inhibitor of MAP2K1 and MAP2K2 known as U0126, blocked MAP2K1, MAP2K2, and MAPK1/3 phosphorylation, inhibited migration, and prevented PDGFA-stimulated migration. These results provide the first insight into the genetic regulation of medulloblastoma metastasis and are the first to suggest a role for and the RAS/MAPK signaling pathway in medulloblastoma metastasis. Inhibitors of PDGFRA and RAS proteins, among others overexpressed M+ genes identified herein, represent novel therapeutic targets in medulloblastomas and other M+/MO tumors. The inventive method of prediction and targeted therapy is applicable to any tumor that exists in both M+ and MO forms, such as the neurotumors glioma, neuroblastoma and ependymoma, as well as lung and breast cancers.

L24 ANSWER 5 OF 10 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004196650 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15094067
TITLE: P66(ShcA) interacts with MAPKAP kinase 2 and regulates its activity.
AUTHOR: Yannoni Yvonne M; Gaestel Matthias; Lin Lih-Ling
CORPORATE SOURCE: Department of Inflammation, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140-2311, USA.. yvonne.yannoni@abbott.com
SOURCE: FEBS letters, (2004 Apr 23) Vol. 564, No. 1-2, pp. 205-11. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20 Apr 2004

Last Updated on STN: 4 Jun 2004
Entered Medline: 3 Jun 2004

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66(ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation.

L24 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:942767 HCAPLUS
DOCUMENT NUMBER: 140:40262
TITLE: Genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics
INVENTOR(S): Nevins, Joseph; West, Mike; Goldschmidt, Pascal
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 408 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091391	A2	20031106	WO 2002-XB38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003091391	A2	20031106	WO 2002-US38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:			
US 2002-374547P	P	20020423
US 2002-420784P	P	20021024
US 2002-421043P	P	20021025
US 2002-424680P	P	20021108
WO 2002-US38221	A	20021112

AB Genes whose expression is correlated with an determinant of an atherosclerotic phenotype are provided. Also provided are methods of using the subject atherosclerotic determinant genes in diagnosis and treatment methods, as well as drug screening methods. In addition, reagents and kits thereof that find use in practicing the subject methods are provided. Also provided are methods of determining whether a gene is correlated with a disease phenotype, where correlation is determined using a Bayesian

anal. [This abstract record is one of three records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L24 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:409169 HCAPLUS
DOCUMENT NUMBER: 138:380506
TITLE: Genes that are differentially expressed during erythropoiesis and their diagnostic and therapeutic uses
INVENTOR(S): Brissette, William H.; Neote, Kuldeep S.; Zagouras, Panayiotis; Zenke, Martin; Lemke, Britt; Hacker, Christine
PATENT ASSIGNEE(S): Pfizer Products Inc., USA; Max-Delbrueck-Centrum Fuer Molekulare Medizin
SOURCE: PCT Int. Appl., 285 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003038130	A2	20030508	WO 2002-XA34888	20021031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003038130	A2	20030508	WO 2002-US34888	20021031
WO 2003038130	A3	20040212		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:		
US 2001-335048P	P	20011031
US 2001-335183P	P	20011102
WO 2002-US34888	A	20021031

AB The present invention provides mol. targets that regulate erythropoiesis. Groups of genes or their encoded gene products comprise panels of the invention and may be used in therapeutic intervention, therapeutic agent screening, and in diagnostic methods for diseases and/or disorders of erythropoiesis. The panels were discovered using gene expression profiling of erythroid progenitors with Affymetrix HU6800 and HG-U95Av2 chips. Cells from an in vitro growth and differentiation system of SCF-Epo dependent human erythroid progenitors, E-cadherin+/CD36+ progenitors, cord blood, or CD34+ peripheral blood stem cells were analyzed. The HU6800 chip contains probes from 13,000 genes with a potential role in cell growth, proliferation, and differentiation and the HG-U95Av2 chip contains 12,000 full-length, functionally-characterized genes. [This abstract record is one of two records for this document necessitated by the large number of index entries required to fully index the

document and publication system constraints.].

L24 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:851837 HCAPLUS
DOCUMENT NUMBER: 141:104117
TITLE: Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease. [Erratum to document cited in CA136:051990]
AUTHOR(S): MacDonald, Tobey J.; Brown, Kevin M.; LaFleur, Bonnie; Peterson, Katia; Lawlor, Christopher; Chen, Yidong; Packer, Roger J.; Cogen, Philip; Stephan, Dietrich A.
CORPORATE SOURCE: Center for Cancer and Transplantation Biology, Children's National Medical Center, Washington, DC, USA
SOURCE: Nature Genetics (2003), 35(3), 287
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The annotation for the Affymetrix G110 probe set 1770 that was used was incorrect. Although the annotation specifies that the transcript for PDGFR-α is being ascertained, the true specificity of the probe set is for the PDGFR-β isoform. The ligand for both receptor isoforms is identical. The functional validation of the PDGFR signaling pathway, described in our article, used specific neutralizing antibodies against PDGFR-α as well as downstream small mol. inhibitors, and it implicates this entire cascade. The PDGFR-β isoform may be more relevant in the metastatic process, but this does not discount the proven biol. role of PDGFR-α and downstream effectors in metastatic medulloblastoma.

L24 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:615889 HCAPLUS
DOCUMENT NUMBER: 137:180730
TITLE: Human cDNA/DNA molecules and proteins encoded by them with enhanced expression in apoptosis-resistant cell clones, and use thereof in diagnosis, therapeutics and drug screening
INVENTOR(S): Ullrich, Axel; Abraham, Reimar
PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V., Germany
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002063037	A2	20020815	WO 2002-EP1073	20020201
WO 2002063037	A3	20031002		
WO 2002063037	A9	20040219		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2434881	A1	20020815	CA 2002-2434881		20020201
AU 2002249170	A1	20020819	AU 2002-249170		20020201
AU 2002249170	B2	20070208			
EP 1364066	A2	20031126	EP 2002-718083		20020201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004517638	T	20040617	JP 2002-562773		20020201
US 2004110177	A1	20040610	US 2003-470845		20030731
AU 2007201963	A1	20070524	AU 2007-201963		20070502
PRIORITY APPLN. INFO.:			US 2001-265631P	P	20010202
			AU 2002-249170	A3	20020201
			WO 2002-EP1073	W	20020201

AB The present invention relates to a method for identifying nucleic acid mols. functionally associated with a desired phenotype, such as cancer cell properties, including anti-apoptosis. The method, which allows for generation of expression profiles of genes associated with said desired phenotype, involves a mutagenesis and/or genome rearrangement step, followed by selection of cell clones displaying the desired phenotype. The invention also relates that the method involves the use of the following techniques: fluorescence-activated cell sorting (FACS); nucleic acid microarray (cDNA, genomic or oligonucleotide); protein array; two-dimensional gel electrophoresis; and/or mass spectrometry. The invention further relates that the disclosed method was used to identify genes, which are differentially expressed in apoptosis-sensitive and apoptosis-resistant cells. Specifically, the invention relates that apoptosis was induced in human cervix carcinoma cell line HeLa S3 by Fas activation. After the selection procedure, only a low number of living cells were present, which had a higher resistance against apoptosis than the parental cell line. MRNA was isolated from these surviving clones, and from the parental cell line, and transcribed into cDNA. CDNA microarray technol. was used to identify about 150-200 genes (cDNA/DNA mols.) that exhibited enhanced expression in apoptosis-resistant clones. The GenBank accession nos. of some of these cDNA/DNA mols. are provided, along with the products encoded by said mols. Still further, the invention relates that most of the apoptosis-associated genes encode protein phosphatases, and kinases. Finally, the invention relates that said nucleic acid mols., and proteins encoded by mols., can be used as targets in diagnosis, therapeutics and drug screening, particularly for disorders associated with dysfunction of apoptotic processes, such as tumors.

L24 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2001:756373 HCAPLUS
DOCUMENT NUMBER:	136:51990
TITLE:	Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease
AUTHOR(S):	MacDonald, Tobey J.; Brown, Kevin M.; LaFleur, Bonnie; Peterson, Katia; Lawlor, Christopher; Chen, Yidong; Packer, Roger J.; Cogen, Philip; Stephan, Dietrich A.
CORPORATE SOURCE:	Center for Cancer and Transplantation Biology, Children's National Medical Center, Washington, DC, USA
SOURCE:	Nature Genetics (2001), 29(2), 143-152 CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER:	Nature America Inc.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Little is known about the genetic regulation of medulloblastoma dissemination, but metastatic medulloblastoma is highly associated with poor outcome. We obtained expression profiles of 23 primary medulloblastomas clin. designated as either metastatic (M+) or non-metastatic (M0) and identified 85 genes whose expression differed significantly between classes. Using a class prediction algorithm based on these genes and a leave-one-out approach, we assigned sample class to these tumors (M+ or

M0) with 72% accuracy and to four addnl. independent tumors with 100% accuracy. We also assigned the metastatic medulloblastoma cell line Daoy to the metastatic class. Notably, platelet-derived growth factor receptor α (PDGFRA) and members of the downstream RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway are upregulated in M+ tumors. Immunohistochem. validation on an independent set of tumors shows significant overexpression of PDGFRA in M+ tumors compared to M0 tumors. Using in vitro assays, we show that platelet-derived growth factor α (PDGFA) enhances medulloblastoma migration and increases downstream MAP2K1 (MEK1), MAP2K2 (MEK2), MAPK1 (p42 MAPK) and MAPK3 (p44 MAPK) phosphorylation in a dose-dependent manner. Neutralizing antibodies to PDGFRA blocks MAP2K1, MAP2K2 and MAPK1/3 phosphorylation, whereas U0126, a highly specific inhibitor of MAP2K1 and MAP2K2, also blocks MAPK1/3. Both inhibit migration and prevent PDGFA-stimulated migration. These results provide the first insight into the genetic regulation of medulloblastoma metastasis and are the first to suggest a role for PDGFRA and the RAS/MAPK signaling pathway in medulloblastoma metastasis. Inhibitors of PDGFRA and RAS proteins should therefore be considered for investigation as possible novel therapeutic strategies against medulloblastoma.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d 1-10 ibib ab kwic

L24 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:121193 HCAPLUS
DOCUMENT NUMBER: 142:214836
TITLE: Biomarkers of cyclin-dependent kinase modulation in cancer therapy
INVENTOR(S): Li, Martha; Rupnow, Brent A.; Webster, Kevin R.; Jackson, Donald G.; Wong, Tai W.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 141 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2005012875	A2	20050210	WO 2004-US24424		20040729
WO 2005012875	A3	20070315			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
AU 2004262369	A1	20050210	AU 2004-262369		20040729
CA 2533803	A1	20050210	CA 2004-2533803		20040729
EP 1656542	A2	20060517	EP 2004-779471		20040729
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR					
JP 2007507204	T	20070329	JP 2006-522045		20040729
US 2007105114	A1	20070510	US 2006-567867		20060818
PRIORITY APPLN. INFO.:			US 2003-490890P	P	20030729
			WO 2004-US24424	W	20040729

AB Biomarkers having expression patterns that correlate with a response of cells to treatment with one or more cdk modulating agents, and uses thereof. Transcription profiling was used to identify the biomarkers. Specifically, transcription profiling of the effect of a certain cdk2 inhibitor (BMS 387032 0.5 L-tartaric acid salt) on peripheral blood mononuclear cells was first performed. Gene chips were used to quantitate the levels of gene expression on a large-scale with Affymetrix human gene chips HG-U95A, B, and C. Next, profiling of a cdk2 inhibitor-treated tumor cell line A28780 at multiple doses and time points was performed to establish a correlation of tumor site response with peripheral blood biomarkers. In order to establish the mol. target-specificity of the potential biomarkers, tumor cell line A2780 treated with anti-cdk2 oligonucleotides was also profiles. Overlapping gene expression changes were selected for further evaluation in human ovarian carcinoma xenograft A2780 that were treated with the cdk2 inhibitor. The selected biomarkers were subjected to real-time PCR anal. in order to verify the observed changes from the gene chip anal. The biomarker comprising GenBank accession number W28729 was discovered to have the most consistent and robust regulation in response to cdk inhibition. Provided are methods for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer that comprises administering an agent that modulates cdk activity.

IT Proteins
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(BTB (POZ) domain containing 3; biomarkers of cyclin-dependent kinase modulation in cancer therapy)

IT Gene, animal
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(MAPKAPK2; biomarkers of cyclin-dependent kinase modulation in cancer therapy)

IT Gene, animal
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(MAPKAPK5; biomarkers of cyclin-dependent kinase modulation in cancer therapy)

L24 ANSWER 2 OF 10 BIOTECHDS COPYRIGHT 2007 THE THOMSON CORP. on STN
DUPLICATE 1
ACCESSION NUMBER: 2004-09118 BIOTECHDS
TITLE: New isolated, purified or recombinant protein complex comprising an MK2 polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc for treating or preventing e.g. Crohn's disease, or rheumatoid arthritis;
involving vector-mediated gene transfer and expression in host cell for use in gene therapy
AUTHOR: LIN L; YANNONI Y M
PATENT ASSIGNEE: WYETH
PATENT INFO: WO 2004012660 12 Feb 2004
APPLICATION INFO: WO 2003-US23981 1 Aug 2003
PRIORITY INFO: US 2002-400044 2 Aug 2002; US 2002-400044 2 Aug 2002
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2004-156998 [15]
AB DERWENT ABSTRACT:
NOVELTY - An isolated, purified or recombinant protein complex comprising a mitogen-activated protein kinase-activated protein kinase 2 (MK2) polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a host cell comprising a first and a second nucleic acid, where the first nucleic acid encodes a recombinant MK2

polypeptide and the second nucleic acid encoding MK2 interacting protein; (2) an assay for determining whether the test compound inhibits or promotes formation of a protein complex; (3) a method for determining whether a test compound affects MK2 activity; (4) an screening assay to identify compounds that inhibit or promote formation of the protein complex; (5) an antibody that binds one or more proteins in the complex; (6) a method for modulating formation of a protein complex in a cell comprising at least a first and a second protein; (7) a method for producing a complex; (8) a drug screening method for identifying anti-inflammatory drugs; (9) a method of modulating inflammation in a tissue; (10) a method of treating or preventing inflammation in a tissue; (11) a method of treating a patient suffering from at least one inflammatory condition; (12) a method of expressing a nucleic acid in a cell to inhibit inflammation; (13) a method of detecting at least one of the absence, presence and amount of MK2 in a sample; (14) a kit that enables qualitative detection of MK2 comprising a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and at least one other kit component chosen from: at least one of buffer and solution; and at least one structural component; and (15) a pharmaceutical composition comprising at least one protein that binds MK2, and at least one carrier.

BIOTECHNOLOGY - Preferred Complex: The protein complex comprises an MK2 polypeptide and at least one or two MK2 interacting protein. The MK2 interacting protein is chosen from STS, HPH2 and Shc. The MK2 polypeptide comprises a fusion protein. The fusion protein comprises a domain for purifying, isolating or detecting the fusion protein. The fusion protein comprises a domain chosen from affinity tags, radionucleotides, enzymes, and fluorophores. The domain is selected from polyhistidine, FLAG, Glu-Glu, glutathione S transferase (GST), thioredoxin, protein A, protein G, and an immunoglobulin heavy chain constant region. Preferred Method: Determining whether a test compound inhibits or promotes formation of a protein complex comprises forming a reaction mixture including an MK2 polypeptide, at least one MK2 interacting protein and the test compound; and detecting the presence of the protein complex between MK2 and the MK2 interacting protein, where a difference in the amount of complex in the presence of the test compound, relative to the amount of complex in the absence of the test compound indicates that the test compound inhibits or promotes complex formation. An increase in the amount of complex in presence of the test compound indicates that the test compound promotes complex formation. A decrease in the amount of complex in presence of the test compound indicates that the test compound inhibits complex formation. Determining whether a test compound affects MK2 activity comprises forming a protein complex comprising an MK2 polypeptide and an MK2 interacting protein; contacting the protein complex with the test compound; and determining the effect of the test compound on one or more activities chosen from MK2 kinase activity, an amount of MK2 in the complex, production of TNF, and amount of phosphorylated form of a substrate of MK2. The screening assay to identify compounds that inhibit or promote formation of a protein complex, comprises providing a two-hybrid assay system including a first fusion protein comprising an MK2 polypeptide, and a second fusion protein comprising a polypeptide chosen from one or more of STS, HPH2 and Shc, under conditions where the two proteins interact in the two hybrid assay system; measuring a level of interaction between the fusion proteins in the presence and in the absence of a test compound; and comparing the level of interaction of the fusion proteins, where a decrease in the level of interaction is indicative of a compound that inhibits the interaction between the MK2 polypeptide and a polypeptide chosen from one or more of STS, HPH2 and Shc. Modulating formation of a protein complex in a cell comprising at least a

first protein and a second protein, where the first protein is an MK2 polypeptide and the second protein is chosen from one or more of STS, HPH2 and Shc, comprises administering to the cell a compound capable of modulating formation of the complex. Producing a complex comprises transfecting a cell with one or more polynucleotides encoding an MK2 polypeptide and an MK2 interacting protein chosen from one or more of STS and Shc, where the polypeptides form a complex. The drug screening method for identifying anti-inflammatory drugs comprises providing MK2 and at least one MK2-interacting protein; allowing MK2 and the protein to interact to form a complex; adding an effective amount of a potential drug to the complex; and determining whether the potential drug inhibits complex formation. The MK2 and the protein interact in vivo in a yeast or mammalian 2-hybrid system. The MK2 and the protein interact in vitro. The protein is STS, Shc or HPH2. The drug is a small molecule, peptide or protein, antibody, or chemical agent. Modulating inflammation in a tissue comprises administering a nucleic acid that encodes an MK2 interacting protein to the tissue; and allowing the nucleic acid to express the MK2 interacting protein, thus to modulate inflammation in the tissue. The nucleic acid expresses a protein chosen from STS, HPH2 and Shc. Treating or preventing inflammation in a tissue comprises administering to the tissue a therapeutically effective amount of at least one agent that blocks the interaction between MK2 and an MK2 interacting protein; or allows the interaction, but blocks MK2 activity. The agent is an antibody, preferably a polyclonal or monoclonal antibody. The antibody binds MK2 or the MK2 -interacting protein. The agent is a chemical agent, a peptide or protein, or a small molecule. Modulating inflammation in a tissue comprises contacting the tissue with at least one protein that binds MK2; and allowing the protein to modulate inflammation in the tissue. Treating a patient suffering from at least one inflammatory condition, comprises administering a therapeutically effective dose of at least one compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the compound to bind to at least one of MK2 or an MK2 complex and modulate inflammation. The protein or peptide is a mutant form of a wild-type protein or peptide, which stimulates MK2 activity. Expressing a nucleic acid in a cell to inhibit inflammation comprises adding at least one nucleic acid encoding a compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the cell to express the compound and inhibit inflammation. Detecting at least one of the absence, presence, and amount of MK2 in a sample, comprises administering at least one compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and correlating the absence, presence, or amount of bound protein or compound with the absence, presence, or amount of MK2 in the sample. Preferred Antibody: The antibody inhibits interaction of MK2 with the MK2 interacting protein. Preferred Kit: The kit further comprises an agent that binds the protein or compound. The agent is an antibody.

ACTIVITY - Antiinflammatory; Gastrointestinal; Antiarthritic; Antirheumatic; Respiratory-Gen; Antiasthmatic; Immunosuppressive; Antiulcer. No biological data given.

MECHANISM OF ACTION - Gene therapy.

USE - The composition and methods are useful for treating or preventing a condition chosen from Crohn's disease, inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, acute respiratory distress syndrome, emphysema, delayed type hypersensitivity reaction,

asthma, systemic lupus erythematosus, and inflammation due to trauma or injury (claimed).

ADMINISTRATION - Dosage is 5-500, preferably 40-60 mg per kg. Administration is intravenous, intramuscular, rectal or subcutaneous.

EXAMPLE - Experimental protocols are described but no results are given. (107 pages)

TI New isolated, purified or recombinant protein complex comprising an MK2 polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc for treating or preventing e.g. Crohn's disease, or rheumatoid arthritis;
involving vector-mediated gene transfer and expression in host cell for. . .

AB DERWENT ABSTRACT:
NOVELTY - An isolated, purified or recombinant protein complex comprising a mitogen-activated protein kinase-activated protein kinase 2 (MK2) polypeptide, and an MK2 interacting protein chosen from STS, HPH2 and Shc, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a host cell comprising a first and a second nucleic acid, where the first nucleic acid encodes a recombinant MK2 polypeptide and the second nucleic acid encoding MK2 interacting protein; (2) an assay for determining whether the test compound inhibits or promotes formation of a protein complex; (3) a method for determining whether a test compound affects MK2 activity; (4) an screening assay to identify compounds that inhibit or promote formation of the protein complex; (5) an antibody. . . a cell to inhibit inflammation; (13) a method of detecting at least one of the absence, presence and amount of MK2 in a sample; (14) a kit that enables qualitative detection of MK2 comprising a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide;. . . and solution; and at least one structural component; and (15) a pharmaceutical composition comprising at least one protein that binds MK2, and at least one carrier.

BIOTECHNOLOGY - Preferred Complex: The protein complex comprises an MK2 polypeptide and at least one or two MK2 interacting protein. The MK2 interacting protein is chosen from STS, HPH2 and Shc. The MK2 polypeptide comprises a fusion protein. The fusion protein comprises a domain for purifying, isolating or detecting the fusion protein. The. . . Determining whether a test compound inhibits or promotes formation of a protein complex comprises forming a reaction mixture including an MK2 polypeptide, at least one MK2 interacting protein and the test compound; and detecting the presence of the protein complex between MK2 and the MK2 interacting protein, where a difference in the amount of complex in the presence of the test compound, relative to the. . . in presence of the test compound indicates that the test compound inhibits complex formation. Determining whether a test compound affects MK2 activity comprises forming a protein complex comprising an MK2 polypeptide and an MK2 interacting protein; contacting the protein complex with the test compound; and determining the effect of the test compound on one or more activities chosen from MK2 kinase activity, an amount of MK2 in the complex, production of TNF, and amount of phosphorylated form of a substrate of MK2. The screening assay to identify compounds that inhibit or promote formation of a protein complex, comprises providing a two-hybrid assay system including a first fusion protein comprising an MK2 polypeptide, and a second fusion protein comprising a polypeptide chosen from one or more of STS, HPH2 and Shc, under conditions where the two proteins interact in the two hybrid assay system; measuring a level of interaction between the. . . proteins, where a decrease in the level of interaction is indicative of a compound that inhibits the interaction between the MK2 polypeptide and a polypeptide

chosen from one or more of STS, HPH2 and Shc. Modulating formation of a protein complex in a cell comprising at least a first protein and a second protein, where the first protein is an MK2 polypeptide and the second protein is chosen from one or more of STS, HPH2 and Shc, comprises administering to the cell a compound capable of modulating formation of the complex. Producing a complex comprises transfecting a cell with one or more polynucleotides encoding an MK2 polypeptide and an MK2 interacting protein chosen from one or more of STS and Shc, where the polypeptides form a complex. The drug screening method for identifying anti-inflammatory drugs comprises providing MK2 and at least one MK2-interacting protein; allowing MK2 and the protein to interact to form a complex; adding an effective amount of a potential drug to the complex; and determining whether the potential drug inhibits complex formation. The MK2 and the protein interact in vivo in a yeast or mammalian 2-hybrid system. The MK2 and the protein interact in vitro. The protein is STS, Shc or HPH2. The drug is a small molecule, peptide or protein, antibody, or chemical agent. Modulating inflammation in a tissue comprises administering a nucleic acid that encodes an MK2 interacting protein to the tissue; and allowing the nucleic acid to express the MK2 interacting protein, thus to modulate inflammation in the tissue. The nucleic acid expresses a protein chosen from STS, HPH2 and Shc. Treating or preventing inflammation in a tissue comprises administering to the tissue a therapeutically effective amount of at least one agent that blocks the interaction between MK2 and an MK2 interacting protein; or allows the interaction, but blocks MK2 activity. The agent is an antibody, preferably a polyclonal or monoclonal antibody. The antibody binds MK2 or the MK2 -interacting protein. The agent is a chemical agent, a peptide or protein, or a small molecule. Modulating inflammation in a tissue comprises contacting the tissue with at least one protein that binds MK2; and allowing the protein to modulate inflammation in the tissue. Treating a patient suffering from at least one inflammatory condition,. . . a therapeutically effective dose of at least one compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and allowing the compound to bind to at least one of MK2 or an MK2 complex and modulate inflammation. The protein or peptide is a mutant form of a wild-type protein or peptide, which stimulates MK2 activity. Expressing a nucleic acid in a cell to inhibit inflammation comprises adding at least one nucleic acid encoding a compound chosen from a compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide;. . . the cell to express the compound and inhibit inflammation. Detecting at least one of the absence, presence, and amount of MK2 in a sample, comprises administering at least one compound that interacts with at least one of MK2 or an MK2 complex, where the compound is chosen from an antibody, a chemical agent, a small molecule, a protein and a peptide; and correlating the absence, presence, or amount of bound protein or compound with the absence, presence, or amount of MK2 in the sample. Preferred Antibody: The antibody inhibits interaction of MK2 with the MK2 interacting protein. Preferred Kit: The kit further comprises an agent that binds the protein or compound. The agent is an. . .

CT RECOMBINANT MK2 PROTEIN PREP., ISOL., VECTOR-MEDIATED GENE TRANSFER, EXPRESSION IN HOST CELL, APPL. INFLAMMATORY BOWEL DISEASE, ULCERATIVE COLITIS, RHEUMATOID ARTHRITIS, ACUTE RESPIRATORY. . . .

L24 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:371064 HCAPLUS

DOCUMENT NUMBER: 140:373461
TITLE: Evaluation of breast cancer states and outcomes using gene expression profiles
INVENTOR(S): West, Mike; Nevins, Joseph R.; Huang, Andrew
PATENT ASSIGNEE(S): Synpac, Inc., USA; Duke University
SOURCE: PCT Int. Appl., 799 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004037996	A2	20040506	WO 2003-US33656	20031024
WO 2004037996	A3	20041229		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004083084	A1	20040429	US 2002-291878	20021112
WO 2004044839	A2	20040527	WO 2002-US38216	20021112
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004106113	A1	20040603	US 2002-291886	20021112
AU 2003284880	A1	20040513	AU 2003-284880	20031024

PRIORITY APPLN. INFO.:			
	US 2002-420729P	P	20021024
	US 2002-421062P	P	20021025
	US 2002-421102P	P	20021025
	US 2002-424701P	P	20021108
	US 2002-424715P	P	20021108
	US 2002-424718P	P	20021108
	US 2002-291878	A	20021112
	US 2002-291886	A	20021112
	US 2002-425256P	P	20021112
	WO 2002-US38216	A	20021112
	WO 2002-US38222	A	20021112
	US 2003-448461P	P	20030221
	US 2003-448462P	P	20030221
	US 2003-457877P	P	20030327
	US 2003-458373P	P	20030331
	WO 2003-US33656	W	20031024

AB The present invention relates generally to a method for evaluating and/or predicting breast cancer states and outcomes by measuring gene and metagene expression levels and integrating such data with clin. risk factors. Genes and metagenes whose expressions are correlated with a particular breast cancer risk factor or phenotype are provided using binary prediction tree modeling. The invention provides 175 genes associated with metagene predictors of lymph node metastasis, 216 genes associated with metagene predictors of breast cancer recurrence, and 496 metagenes related

to breast cancer study. Methods of using the subject genes and metagenes in diagnosis and treatment methods, as well as drug screening methods, etc are also provided. In addition, reagents, media and kits that find use in practicing the subject methods are also provided.

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(MAPKAPK2; evaluation of breast cancer states and outcomes using gene expression profiles)

IT Proteins
RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(SHC; evaluation of breast cancer states and outcomes using gene expression profiles)

IT 9001-40-5, Glucose-6-phosphate dehydrogenase 9014-51-1, Indoleamine 2,3-dioxygenase 9023-44-3, Tryptophanyl-tRNA synthetase 9026-52-2, Mevalonate kinase 9026-67-9, Choline kinase 9026-92-0, DCMP deaminase 9028-69-7, 5,10-Methylenetetrahydrofolate reductase 9029-62-3, Squalene epoxidase 9031-61-2, Thymidylate synthetase 9050-76-4, RNase H2 9059-11-4, Amine oxidase 9067-69-0, [Blood group substance] α-acetylgalactosaminyltransferase 9068-57-9, Acrosin 37205-63-3, ATP synthase 37259-83-9, Hexose-6-phosphate dehydrogenase 37277-82-0, Spermidine synthase 37289-06-8, N-Acylsphingosine amidohydrolase 37289-19-3, GTP cyclohydrolase 1 37289-41-1, N-Sulfoglucosamine sulfohydrolase 50936-59-9, Iduronate 2-sulfatase 65666-35-5, Galactosamine-6-sulfate sulfatase 65997-74-2, Cathepsin F 74812-43-4, Spermine synthase 74812-49-0, Ubiquitin protein ligase 81627-83-0, Colony stimulating factor 1 83380-83-0, Esterase D 91608-96-7, Double-stranded RNA-dependent protein kinase 92941-56-5, Arylalkylamine N-acetyltransferase 105238-46-8, Macropain 141588-26-3, Leukocyte tyrosine kinase 141760-45-4, Furin 143180-74-9, Granzyme B 146838-30-4, MAPKAPK2 148710-29-6, Aflatoxin aldehyde reductase 157482-36-5, Janus kinase 3 178037-70-2, Gene sgk protein kinase 182762-08-9, Caspase 4 184049-62-5, Protein phosphatase MKP3 189767-90-6 191808-15-8, 3-Phosphoinositide dependent protein kinase 1 196622-94-3, Granzyme K 196718-00-0, Decysin 271597-10-5, Growth differentiation factor 1 334758-14-4, Cytochrome P 450 4F12 342900-22-5, Kallikrein 11 342900-44-1, Kallikrein 13 377734-62-8, Granulysin 400653-84-1, Dual specificity protein phosphatase 8 440363-51-9, Cytochrome P 450 2A13 458560-40-2, Protein kinase STK6
RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(evaluation of breast cancer states and outcomes using gene expression profiles)

L24 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:533778 HCAPLUS
DOCUMENT NUMBER: 141:65087
TITLE: Gene expression-based method for distinguishing metastatic from non-metastatic forms of a tumor, and use in designing therapeutic drugs
INVENTOR(S): Stephan, Dietrich A.; MacDonald, Tobey J.; Brown, Kevin M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 17 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004126755	A1	20040701	US 2001-940454	20010829

PRIORITY APPLN. INFO.: US 2001-940454 20010829

AB Gene expression profiling of tumors, clin. designated as either metastatic (M+) or non-metastatic (M0), identifies genes whose expression differed significantly between classes. A class-prediction algorithm based on these medulloblastoma genes assigned the sample class to these tumors (M+ or M0) with 72% accuracy and to four addnl. independent tumors with a 100% accuracy. Class prediction also assigned the metastatic medulloblastoma cell line Daoy to the metastatic class. Notably upregulated in the M+ tumors were platelet derived growth factor receptor alpha (PDGFRA) and members of the downstream RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway. Immunohistochem. validation on an independent set of tumors showed significant overexpression of PDGFRA in M+ tumors as compared to M0 tumors. In in vitro assays, PDGFA enhanced medulloblastoma migration and increased downstream MAP2K1 (MEK1), MAP2K2 (MEK2), MAPK1 (p42 MAPK), and MAPK3 (p44 MAPK) phosphorylation in a dose-dependent manner. Neutralizing antibodies to PDGFRA or U0126, a highly specific chemical inhibitor of MAP2K1 and MAP2K2 known as U0126, blocked MAP2K1, MAP2K2, and MAPK1/3 phosphorylation, inhibited migration, and prevented PDGFA-stimulated migration. These results provide the first insight into the genetic regulation of medulloblastoma metastasis and are the first to suggest a role for and the RAS/MAPK signaling pathway in medulloblastoma metastasis. Inhibitors of PDGFRA and RAS proteins, among others overexpressed M+ genes identified herein, represent novel therapeutic targets in medulloblastomas and other M+/MO tumors. The inventive method of prediction and targeted therapy is applicable to any tumor that exists in both M+ and MO forms, such as the neurotumors glioma, neuroblastoma and ependymoma, as well as lung and breast cancers.

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SHC; gene expression-based method for distinguishing metastatic from non-metastatic tumors, and use in designing therapeutic drugs)

IT 9012-90-2, DNA polymerase 9013-66-5, Glutathione peroxidase 9025-26-7, Cathepsin D 9027-03-6, Ubiquinol cytochrome c reductase 9032-68-2, Cathepsin C 9035-51-2, Cytochrome P 450, biological studies 9035-54-5, Placental lactogen 37353-41-6, Cysteine protease 50812-37-8, Glutathione S-transferase 74812-49-0 80449-02-1, Tyrosine kinase 83268-44-4 86102-31-0, TIMP 115926-52-8, PI 3-kinase 127464-60-2, Vascular endothelial growth factor 141436-78-4, Protein kinase C 142008-29-5, CAMP-dependentprotein kinase 142243-02-5, Mitogen-activated protein kinase 142805-58-1, MEK1 kinase 148348-15-6, Fibroblast growth factor 7 148640-14-6, Rac protein kinase 149885-84-7, Dual-specificity protein phosphatase 150316-14-6, MEK2 kinase 151769-16-3, TNF-α-converting enzyme 161052-08-0, Tie receptor tyrosine kinase 289898-51-7, Jnk1 kinase 377752-08-4, Ribosomal protein S6 kinase 2 397251-44-4, MAPKAP kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression-based method for distinguishing metastatic from non-metastatic tumors, and use in designing therapeutic drugs)

L24 ANSWER 5 OF 10 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004196650 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15094067
TITLE: P66(ShcA) interacts with MAPKAP kinase 2 and regulates its activity.
AUTHOR: Yannoni Yvonne M; Gaestel Matthias; Lin Lih-Ling
CORPORATE SOURCE: Department of Inflammation, Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140-2311, USA.. yvonne.yannoni@abbott.com
SOURCE: FEBS letters, (2004 Apr 23) Vol. 564, No. 1-2, pp. 205-11. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200406
ENTRY DATE: Entered STN: 20 Apr 2004
Last Updated on STN: 4 Jun 2004
Entered Medline: 3 Jun 2004

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66(ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation.

TI P66(ShcA) interacts with MAPKAP kinase 2 and regulates its activity.

AB Three mitogen activated protein kinase-activated protein kinase 2 (MAPKAP kinase 2, MK2) interacting proteins were identified using a yeast two-hybrid approach. ShcA, a signaling phospho-protein, human polyhomeotic 2 (HPH2), a transcriptional regulator, and highly similar to smoothelin (HSTS), which is related to the cytoskeletal associated protein smoothelin, interact specifically with MK2. The interaction of MK2 with the 66 kDa isoform of ShcA, p66(ShcA), and HPH2 was confirmed using co-immunoprecipitation. MK2 is activated with p66(ShcA) co-expression and p66(ShcA) is an in vitro substrate for MK2, further demonstrating their association and suggesting a biological role for p66(Shc) in MK2 activation.

L24 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:942767 HCAPLUS
DOCUMENT NUMBER: 140:40262
TITLE: Genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics
INVENTOR(S): Nevins, Joseph; West, Mike; Goldschmidt, Pascal
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 408 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091391	A2	20031106	WO 2002-XB38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003091391	A2	20031106	WO 2002-US38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-374547P P 20020423
US 2002-420784P P 20021024
US 2002-421043P P 20021025
US 2002-424680P P 20021108
WO 2002-US38221 A 20021112

AB Genes whose expression is correlated with an determinant of an atherosclerotic phenotype are provided. Also provided are methods of using the subject atherosclerotic determinant genes in diagnosis and treatment methods, as well as drug screening methods. In addition, reagents and kits thereof that find use in practicing the subject methods are provided. Also provided are methods of determining whether a gene is correlated with a disease phenotype, where correlation is determined using a Bayesian anal. [This abstract record is one of three records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IT 444967-60-6 444967-64-0 444967-94-6 444968-02-9 444968-33-6 445046-93-5 445046-97-9, Keratin 18 (human gene KRT18) 445047-05-2 445047-24-5 445047-26-7 445047-27-8 459481-13-1 459483-00-2, Protein (human 461-amino acid) 459483-69-3, GenBank AAA35587 459485-04-2 459488-59-6 459488-70-1 459490-09-6 459492-63-8, GenBank CAA80258 459499-49-1 459501-90-7, GenBank BAA09534 459503-60-7 459503-76-5 459504-00-8, GenBank AAC51926 459504-82-6, GenBank AAC33794 459504-86-0 459506-17-3, GenBank BAA76810 459509-52-5 459511-39-8 459512-24-4, GenBank BAA00472 459512-52-8, Protein (human 364-amino acid) 459512-91-5, Protein (human 346-amino acid) 459513-03-2 459513-39-4, Protein (human 145-amino acid) 459513-52-1, GenBank CAA26203 459513-68-9, Protein (human gene LYN) 459514-36-4, GenBank AAA59482 459515-65-2, GenBank AAA51554 459516-86-0, GenBank CAA26306 459517-04-5, Protein (human 437-amino acid) 459518-52-6 459518-75-3, GenBank AAA60964 459519-13-2 459519-50-7 459520-26-4, Laminin (human gene LAMB2 B2 chain) 459520-72-0 459521-00-7, Protein 14.3.3 (human Jurkat cell) 459521-43-8 459522-09-9 459522-11-3, GenBank AAA03476 459522-98-6, HLA-DMB (human) 459523-02-5 459523-19-4 459523-82-1, GenBank AAC51320 459524-46-0, Iron regulatory factor (human) 459524-52-8, 14-3-3 Protein (human clone hBM5) 459525-21-4 459525-39-4, GenBank CAA46050 459525-94-1 459526-16-0 459526-47-7, GenBank CAA47471 459526-75-1, GenBank AAB92356 459527-67-4, GenBank AAA60119 459527-77-6, GenBank AAA64378 459528-09-7, Tyrosine kinase (human) 459528-15-5 459528-29-1, Protein (human gene GPI-H) 459528-40-6 459528-84-8 459529-18-1, GenBank CAA69661 459529-19-2 459529-41-0, GenBank AAC69993 459530-67-7, GenBank CAB17043 459530-75-7 459531-22-7, GenBank AAA18019 459531-41-0, Ceramidase, glucosyl- (human gene GBA) 459531-45-4 459531-65-8, GenBank BAA08453 459531-84-1 459531-92-1, Protein (human gene gas1) 459531-98-7, Protease M (human) 459532-05-9, GenBank AAA18945 459532-14-0, GenBank BAA05462 459532-38-8 459534-37-3, GenBank CAA56042 459534-40-8, GenBank AAC50476 459535-05-8, GenBank BAA28707 459535-14-9, LPAP (human) 459535-29-6 459535-48-9 459535-52-5 459535-64-9 459535-85-4 459536-73-3, GenBank CAA53712 459536-74-4, DAP-1 (human cell line HL-60 gene DAP-1) 459536-84-6, Cell surface glycoprotein (human) 459537-01-0 459537-18-9, Protein HFcRn (human clone 11/3) 459537-72-5 459537-77-0, Integrin alpha 8 subunit (human) 459537-99-6 459538-25-1 459538-57-9, GenBank AAB60402 459538-91-1, PRK2 (human) 459539-55-0, Prostasin (human strain Caucasian) 459539-64-1, GenBank CAB43367 459540-34-2, GenBank CAA56491 459541-99-2, A-Glucosidase I (human) 459542-37-1, P56lck (human cell line Molt-4 gene lck) 459543-08-9, GenBank CAA61447 459543-11-4 459543-14-7, GenBank AAA86686 459543-23-8 459543-60-3, GenBank AAB07513 459543-65-8, GenBank

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459609-20-2, GenBank AAB83960 459609-62-2 459609-75-7, Protein (human
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GenBank BAA24056 . 459610-19-6 459610-21-0 459612-12-5, GenBank
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GenBank AAB97735 459615-21-5, SPOP (human cell line HeLa) 459616-27-4
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459620-44-1, GenBank AAC39694
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(amino acid sequence; genes expressed in atherosclerotic tissue and
their use in diagnosis and pharmacogenetics)

IT 480930-64-1 480930-65-2, GenBank AAC19160 480931-06-4 480931-07-5
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GenBank AAC28648 480933-99-1, GenBank AAC28886 480934-39-2, RIP
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(human clone BAC 203o13) 480935-48-6, KIAA0345-like 4 (human clone BAC 203o13) 480935-49-7 480935-50-0, KIAA0345-like 6 (human clone BAC 203o13) 480935-51-1, KIAA0345-like 7 (human clone BAC 203o13) 480935-52-2, KIAA0345-like 8 (human clone BAC 203o13) 480935-53-3, KIAA0345-like 9 (human clone BAC 203o13) 480935-54-4 480935-55-5 480935-56-6 480935-57-7 480935-92-0, SPF31 (human cell line HeLa gene SPF31) 480935-97-5 480936-38-7 480936-90-1 480937-06-2, Protein (human gene NAP) 480937-21-1, Enigma protein (human cell line SKNMC) 480937-35-7 480937-86-8 480938-25-8, GenBank AAC39735 480938-40-7, GenBank AAC39785 480938-64-5 480938-75-8, Kallistatin (human gene PI4) 480939-16-0 480941-44-4 480941-62-6 480942-02-7 480942-28-7 480942-46-9, GenBank AAC50203 480942-48-1, GenBank AAC50206 480942-49-2, PRK1 (human) 480942-56-1 480942-57-2 480942-58-3, GenBank AAC50226 480942-75-4 480943-31-5 480943-34-8, Nucleoporin 98 (human gene NUP98) 480943-48-4, IL-1Rrp (human) 480943-69-9 480943-80-4, Dystrobrevin-epsilon (human) 480943-91-7, Alpha1-syntrophin (human gene SNT A1) 480943-92-8, UHX1 protein (human gene UHX1) 480944-04-5 480944-53-4, GenBank AAC50567 480944-54-5, Semaphorin (human clone lambda 5) 480944-81-8 480944-89-6 480944-93-2, GenBank AAC50642 480944-94-3 480945-59-3 480945-62-8, GenBank AAC50826 480946-22-3, GenBank AAC50933 480946-23-4, Acetolactate synthase (human) 480946-82-5 480950-79-6 480952-85-0 480953-57-9, GenBank AAC62004 480953-64-8, GenBank AAC62258 480953-65-9, GenBank AAC62259 480953-75-1 480953-78-4 480953-95-5, Protein (human gene LNHR) 480956-15-8, GenBank AAC70912 480956-18-1 480956-20-5, GenBank AAC71082 480956-22-7, MSE55-related protein (human gene UB1) 480958-08-5, Protein (human clone 558 99-amino acid) 480958-11-0, GenBank AAC72949 480958-14-3, Protein (human clone 628 286-amino acid) 480958-15-4, Protein (human clone 638 127-amino acid) 480958-16-5, Protein (human clone 638 198-amino acid) 480958-20-1, Protein (human clone 669 175-amino acid) 480958-31-4 480958-58-5 480958-70-1, Alpha SNAP (human) 480959-05-5 480959-07-7 480959-35-1 480959-37-3, HMG box factor SOX-13 (human) 480959-52-2, DB1 (human cell line jurkat clone DB15) 481119-03-3, GenBank AAC95470 481123-33-5 481123-58-4 481123-63-1, Beta-arrestin 2 (human) 481123-77-7 481123-78-8 481125-70-6, Serine protease (human clone 10.16) 481126-30-1, Neuralized (human) 481126-33-4, GenBank AAD01900 481126-51-6 481126-81-2, 7-60 (Human) 481126-84-5, AP-3 complex sigma3A subunit (human) 481127-24-6 481128-21-6, MAPKAP kinase (human clone 3pK gene 3pK) 481128-88-5 481128-91-0, GenBank BAA24500 481129-08-2, GenBank BAA23417 481129-09-3 481129-24-2 481129-31-1 481129-32-2 481129-36-6 481129-38-8 481129-41-3 481129-42-4 481129-46-8 481129-56-0 481130-79-4, Cadherin FIB1 (human) 481130-89-6 481130-90-9 481130-95-4, Protein (human gene HRIHFB2018) 481131-19-5, Protein MD-1 (human) 481131-72-0, GenBank BAA19055 481131-74-2 481131-82-2 481132-39-2 481132-98-3, GenBank BAA23647 481133-18-0 481133-58-8, Galectin-3 (human clone HP01100) 481133-60-2, Galectin-9 isoform (human clone HP01461) 481133-63-5 481133-65-7 481133-68-0 481133-71-5, GenBank BAA25480 481134-11-6 481134-18-3 481134-97-8 481135-03-9 481135-04-0 481135-05-1 481135-34-6 481135-38-0 481135-43-7 481136-02-1 481136-21-4, Protein (human gene DP-2) 481136-84-9, 14-3-3 Protein eta chain (human) 481137-21-7 481137-22-8 481137-52-4 481137-56-8, GenBank AAA69698 481138-71-0 481138-72-1 481139-04-2, Protein (human clone HEPCR1 gene EP3-IV) 481139-05-3 481139-22-4, Histidase (human) 481139-86-0 481140-40-3 481140-84-5 481140-87-8 481140-91-4 481140-93-6, Transcriptional activator hSNF2a (human) 481141-06-4, Protoporphyrinogen oxidase (human) 481141-16-6 481141-17-7, GenBank BAA09483 481141-20-2 481141-25-7 481141-26-8 481142-20-5 481142-62-5, Calgranulin C (human) 481143-12-8 481143-13-9 481143-15-1 481143-32-2 481143-51-5 481143-53-7 481143-55-9 481143-74-2 481143-79-7 481144-23-4, GenBank BAA05789 481144-72-3 481146-03-6 481146-06-9 481146-40-1, Cysteinyl-tRNA synthetase (human) 481146-65-0 481146-90-1, Zinc finger protein FPM315 (human) 481147-44-8 481147-63-1, AMY (human cell line IMR-32)

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481148-67-8, Nramp (human clone Nramp8) 481148-83-8, GenBank BAA82509
481148-98-5 481149-02-4 481149-12-6 481149-61-5, CRK-II (human)
481149-78-4 481149-83-1, Neuroblastoma (human gene nbr) 481149-92-2
481149-98-8 481150-07-6, ORF (human) 481150-08-7 481150-25-8,
Pre-granzyme 3 (human) 481150-42-9 481150-56-5 481150-71-4
481150-73-6 481150-99-6, Acid sphingomyelinase (human gene SMPD1)
481151-00-2, Acid sphingomyelinase (human gene SMPD1) 481151-01-3,
Protein (human 102-amino acid) 481151-02-4, Protein (human 104-amino
acid) 481151-03-5, Protein (human gene SMPD1) 481151-71-7
481151-76-2 481151-81-9
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(amino acid sequence; genes expressed in atherosclerotic tissue and
their use in diagnosis and pharmacogenetics)

L24 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:409169 HCAPLUS
DOCUMENT NUMBER: 138:380506
TITLE: Genes that are differentially expressed during erythropoiesis and their diagnostic and therapeutic uses
INVENTOR(S): Brissette, William H.; Neote, Kuldeep S.; Zagouras, Panayiotis; Zenke, Martin; Lemke, Britt; Hacker, Christine
PATENT ASSIGNEE(S): Pfizer Products Inc., USA; Max-Delbrueck-Centrum Fuer Molekulare Medizin
SOURCE: PCT Int. Appl., 285 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003038130	A2	20030508	WO 2002-XA34888	20021031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003038130	A2	20030508	WO 2002-US34888	20021031
WO 2003038130	A3	20040212		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:		
US 2001-335048P	P	20011031
US 2001-335183P	P	20011102
WO 2002-US34888	A	20021031

AB The present invention provides mol. targets that regulate erythropoiesis.

Groups of genes or their encoded gene products comprise panels of the invention and may be used in therapeutic intervention, therapeutic agent screening, and in diagnostic methods for diseases and/or disorders of erythropoiesis. The panels were discovered using gene expression profiling of erythroid progenitors with Affymetrix HU6800 and HG-U95Av2 chips. Cells from an in vitro growth and differentiation system of SCF-Epo dependent human erythroid progenitors, E-cadherin+/CD36+ progenitors, cord blood, or CD34+ peripheral blood stem cells were analyzed. The HU6800 chip contains probes from 13,000 genes with a potential role in cell growth, proliferation, and differentiation and the HG-U95Av2 chip contains 12,000 full-length, functionally-characterized genes. [This abstract record is one of two records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IT 459518-11-7, GenBank CAA61579 459518-51-5 459518-52-6 459518-87-7, G-Protein β-3 chain (human gene GNB3) 459519-04-1 459519-11-0, Protein (human 586-amino acid) 459519-31-4 459519-47-2, GenBank CAA38401 459519-50-7 459519-86-9 459520-02-6 459520-15-1 459520-60-6, GenBank AAA03652 459520-72-0 459520-85-5, Nuclear autoantigen (human gene Sp-100) 459521-00-7, Protein 14.3.3 (human Jurkat cell) 459521-60-9 459521-62-1, Arnt (human cell line HepG2 gene ARNT) 459521-86-9 459521-96-1, Protein (human clone G16 345-amino acid) 459522-07-7, GenBank AAA35860 459522-10-2, GenBank CAB56794 459522-11-3, GenBank AAA03476 459522-20-4 459522-79-3, GenBank CAB02541 459522-84-0 459522-94-2, GenBank CAA40016 459522-95-3, Moesin B (human cell HL 60) 459522-98-6, HLA-DMB (human) 459523-01-4 459523-02-5 459523-06-9, GenBank AAC78725 459523-18-3, GenBank AAA16105 459523-19-4 459523-43-4, Phosphate carrier protein (human) 459523-47-8, GenBank AAA59531 459523-58-1 459523-95-6 459524-17-5, Protein (human gene PGM1) 459524-29-9, GenBank AAA35641 459524-46-0, Iron regulatory factor (human) 459524-52-8, 14-3-3 Protein (human clone hBM5) 459525-65-6 459525-88-3, ATPase (human) 459525-94-1 459526-16-0 459526-33-1 459526-46-6, GenBank CAA49189 459526-75-1, GenBank AAB92356 459527-06-1, GenBank CAA47285 459527-66-3, GenBank CAA78475 459528-15-5 459528-29-1, Protein (human gene GPI-H) 459528-38-2, GenBank AAC50130 459528-44-0, GenBank AAA36729 459528-71-3, Protein (human gene AF-9) 459528-72-4, Protein (human gene AF-4) 459528-84-8 459529-02-3, GenBank AAB02036 459529-44-3 459530-14-4, Protein p78 (human gene p78) 459530-41-7 459530-42-8, GenBank CAA46519 459531-45-4 459531-84-1 459531-91-0 459532-05-9, GenBank AAA18945 459532-32-2, GenBank CAA59689 459532-38-8 459532-55-9, GenBank AAA36443 459532-58-2, GenBank AAA19251 459532-87-7, GenBank CAA54417 459533-17-6, GenBank CAA63295 459533-28-9 459533-74-5, GenBank AAB40977 459534-62-4, GenBank CAA73107 459534-79-3, GenBank AAA59187 459535-03-6, GenBank CAA56730 459535-11-6, Protein p84 (human clone N5-4) 459535-29-6 459535-48-9 459535-52-5 459535-64-9 459535-67-2, GenBank AAB88724 459536-19-7 459536-28-8, GenBank AAA81905 459536-29-9 459536-66-4, ALDH7 (human clone ALDH7) 459536-74-4, DAP-1 (human cell line HL-60 gene DAP-1) 459536-84-6, Cell surface glycoprotein (human) 459536-88-0 459536-90-4 459537-18-9, Protein HFcRn (human clone 11/3) 459537-57-6, GenBank CAA99732 459538-25-1 459538-37-5, GenBank AAA03192 459538-91-1, PRK2 (human) 459539-00-5, GenBank CAA63224 459539-55-0, Prostasin (human strain Caucasian) 459540-22-8, FXR1 (human) 459540-27-3 459540-33-1, GenBank CAA56489 459540-34-2, GenBank CAA56491 459541-39-0, GenBank AAA80581 459541-60-7 459541-83-4, GenBank AAB96827 459541-99-2, A-Glucosidase I (human) 459542-16-6, Protein (human clone 126 gene DR-nm-23) 459542-21-3 459542-26-8 459542-28-0, CDK8 protein kinase (human gene CDK8) 459542-52-0 459542-79-1, GenBank AAC50205 459543-02-3, GenBank AAA91458 459543-14-7, GenBank AAA86686 459543-17-0, GenBank CAA65633 459543-31-8, GenBank AAC50294 459543-60-3, GenBank AAB07513 459543-66-9, GenBank AAC50289 459543-68-1, GenBank AAB36088 459543-74-9, Dihydropyrimidine dehydrogenase (human) 459548-52-8, HPMSR6 (human gene hPMSR6)

459548-58-4, GenBank AAC50292 459548-78-8, GenBank CAA60384
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459549-69-0 459549-73-6, Yeast sds-22 (human gene sds-22) 459549-85-0
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459550-67-5, GenBank AAC16912 459550-74-4, P126 (Human gene ST5)
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(human) 459551-64-5, GenBank AAC50433 459551-65-6, Antisecretory
factor-1 (human) 459552-32-0, GenBank CAA63418 459552-43-3, SMT3B
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459556-11-7, GenBank CAA63069 459556-21-9, GenBank AAC05330
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459562-85-7, GenBank AAC50695 459576-39-7 459576-40-0, SMT3C protein
(human gene SMT3C) 459576-70-6, GenBank AAB36871 459577-04-9, GenBank
AAB49751 459577-11-8, GenBank AAB18823 459577-23-2, Ste-20-like kinase
(human) 459577-30-1 459577-55-0, Ubiquitin hydrolase (human gene
DFFRX) 459577-66-3, FX (human) 459577-70-9, GenBank AAB07689
459577-71-0, GenBank AAC50731 459578-19-9, GenBank AAB05814
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AAB46370 459579-18-1, GenBank AAB36682 459579-29-4, GenBank CAA57478
459579-54-5 459579-93-2, Ataxin 2 (human gene SCA2) 459580-08-6,
Protein CGR19 (human clone hCGR19) 459580-36-0, YMP (human gene YMP)
459580-37-1 459580-45-1, GenBank CAA68851 459580-57-5, GenBank
AAA62269 459580-63-3, CC chemokine STCP-1 (human) 459580-66-6, GenBank
AAC50898 459580-98-4 459581-12-5, Protein (human gene OLF3)
459581-20-5 459581-85-2, TIF1-beta zinc finger protein (human)
459581-86-3, GenBank AAB51517 459582-00-4, GenBank AAB42217
459582-04-8, GenBank CAA55356 459582-06-0, GenBank AAB41495
459582-07-1, Osteoclast stimulating factor (human) 459582-40-2
459582-44-6, Kinase Myt-1 (human gene Myt-1) 459582-46-8, GenBank
CAA64670 459582-49-1 459582-52-6, GenBank AAC50995 459583-84-7,
GenBank AAC51127 459584-48-6, Bikunin (human) 459584-81-7, GenBank
AAB49031 459584-97-5 459585-04-7 459585-15-0, GenBank AAC51173
459585-24-1, Aminopeptidase (human) 459585-28-5, GenBank AAB51514
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459585-84-3, P66-Shc (human gene SHC) 459585-90-1,
C8 (Human gene C8) 459585-91-2, C9 (Human gene C9) 459585-92-3, B7
(Human gene B7) 459585-93-4, DRPLA (human gene HUMDRPLA1) 459585-95-6,
C2f (Human gene C2f) 459585-96-7, GenBank AAC51640 459585-97-8, C3f
(Human gene C3f) 459586-22-2
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(amino acid sequence; genes that are differentially expressed during erythropoiesis and their diagnostic and therapeutic uses)

IT 480943-69-9 480943-73-5, Dynamitin (human) 480943-77-9 480943-82-6,
Trans-Golgi p230 (human) 480943-92-8, UHX1 protein (human gene UHX1)
480943-99-5, Ikaros/LyF-1 (human gene hIk-1) 480944-04-5 480944-06-7,
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TSC-22 protein (human) 480944-71-6 480944-83-0, VHL binding protein-1

(human gene VBP-1) 480944-89-6 480944-94-3 480945-09-3 480945-16-2 480945-17-3, DNA polymerase gamma (human) 480945-22-0, STAM (human) 480945-59-3 480945-60-6 480946-15-4, NifU-like protein (human gene hNifU) 480946-16-5 480946-17-6, GenBank AAC50889 480946-18-7, FUSE binding protein 3 (human gene FBP3) 480946-20-1, Soluble protein Jagged (human) 480946-23-4, Acetolactate synthase (human) 480947-84-0 480947-92-0, Menin (human gene MEN1) 480947-93-1, Menin (human gene MEN1) 480947-94-2, HsPex7p (human gene HsPEX7) 480948-05-8, C2H2-150 (human) 480948-06-9, GenBank AAC51298 480948-23-0, CREB-binding protein (human clone cRT16) 480948-30-9, Phosphomannomutase (human gene PMM2) 480948-31-0 480950-79-6 480950-82-1, Zinc finger protein (human clone PRD51) 480952-54-3 480952-92-9 480953-02-4, P43 (human gene P43) 480953-78-4 480954-49-2, GenBank AAC64483 480958-41-6, Protein MRE11 (human) 480958-70-1, Alpha SNAP (human) 480959-26-0, Tryptase-I (human) 481118-85-8 481123-85-7, PP35 (human) 481123-88-0 481123-89-1 481123-95-9, No arches (human gene nar) 481125-18-2 481126-83-4, AP-3 complex delta subunit (human) 481126-84-5, AP-3 complex sigma3A subunit (human) 481128-21-6, MAPKAP kinase (human clone 3pK gene 3pK) 481128-47-6, DPH2L (human clone B2-3.1) 481128-88-5 481128-89-6, GenBank AAA66020 481128-90-9 481129-09-3 481132-23-4 481135-33-5, Cystic fibrosis antigen (human) 481135-38-0 481135-94-8 481135-96-0 481136-09-8 481136-21-4, Protein (human gene DP-2) 481137-32-0 481137-54-6 481137-57-9 481138-63-0 481138-95-8, Protein (human gene CD19) 481143-79-7 481145-07-7 481150-24-7 481150-30-5 481150-42-9 481150-53-2, Sulfite oxidase (human) 481150-87-2 481151-66-0 481151-93-3 481151-94-4 481152-07-2, HPAK65 (human gene hPAK65) 481152-10-7, Elongin A (human clone pSPORT 1) 481152-79-8 481152-80-1 481153-08-6 481153-10-0 481157-48-6 481158-22-9 481158-89-8, Trophinin (human clone HTH55) 481158-91-2, DNA binding protein (human gene HPF2) 481167-58-2 481168-59-6 481168-67-6, 100 KDa coactivator (human) 481168-68-7, L-iditol-2 dehydrogenase (human) 481168-69-8, L-iditol-2 dehydrogenase (human) 481169-13-5, Lamin B2 (human gene LAMB2) 481169-39-5 481169-76-0, GenBank AAA82559 481169-84-0 481170-45-0 481170-75-6, P57KIP2 (human gene KIP2) 481170-93-8, B4-2 protein (human clone B4-2) 481170-95-0 481171-13-5 481171-27-1 481171-28-2, Csa-19 (human) 481171-35-1 481171-86-2 481171-88-4 481171-93-1 481172-22-9 481172-35-4, Protein (human 83-amino acid) 481172-57-0, Glycophorin A (human gene GYPA) 481172-64-9 481172-65-0 481172-87-6 481172-88-7 481172-93-4 481172-94-5 481173-21-1, UV-damaged DNA binding factor (human) 481173-32-4 481173-36-8 481173-38-0 481173-44-8 481173-48-2, Protein (human gene DSS1) 481173-55-1, HnRNP H (human cell line MRC-5 V2) 481173-60-8 481173-61-9, UbcH5B (human gene UBCH5B) 481173-62-0, UbcH5C (human gene UBCH5C) 481173-69-7, Tis11d (human) 481173-72-2 481173-78-8 481173-96-0 481173-98-2 481174-26-9 481174-31-6, PL6 protein (human clone PL6 gene PL6) 481174-49-6, Protein (human gene LYL1) 481174-55-4 481174-61-2 481174-62-3 481174-68-9 481174-76-9, SRp40-1 (human gene SRp40) 481174-77-0 481175-06-8 481175-07-9, Transcription factor (human gene MEF2) 481175-18-2 481175-34-2, Protein (human gene FRG1) 481175-37-5 481175-41-1 481175-66-0, Protein (human 387-amino acid) 481175-93-3 481176-07-2, CREB-RP (human gene creb-rp) 481176-08-3, HPMSR2 (human gene hPMSR2) 481176-09-4, HPMSR3 (human gene hPMSR3) 481176-11-8, Protein (human gene TCTA) 481176-26-5, ZNF157 (human gene ZNF157) 481176-30-1, Adenosine kinase (human) 481176-61-8 481176-63-0, Frataxin (human gene FRDA) 481177-04-2 481177-06-4, Calbindin 27 (human) 481177-17-7 481177-18-8 481178-43-2, Protein (human clone LUCA15 gene LUCA15) 481178-48-7, Prolylcarboxypeptidase (human) 481178-67-0 481178-97-6, E2F-5 (human) 481179-50-4, Protein (human gene HEXA) 481179-57-1 481179-64-0, Dihydrolipoamide dehydrogenase (human) 481179-98-0, Deoxyhypusine synthase (human) 481179-99-1 481180-02-3 481180-14-7, Protein phosphatase-1 inhibitor (human) 481180-44-3 481180-45-4 481180-56-7, Protein (human 329-amino acid) 481180-57-8, Protein (human 232-amino acid) 481180-61-4 481181-27-5 481181-45-7 481181-57-1

481182-47-2, Protein G0S2 (human gene G0S2) 481182-64-3 481182-72-3 481183-02-2 481183-06-6 481183-14-6 481183-32-8 481183-49-7, CALM (human gene CALM) 481183-51-1 481183-72-6, Glutaryl-CoA dehydrogenase (human) 481184-01-4, P2X5a (human) 481184-05-8 481184-11-6 481184-22-9 481186-99-6 481188-52-7, 2,4-Dienoyl-CoA reductase (human) 481188-53-8 481195-74-8 481195-80-6, MAP kinase kinase MEK5b (human) 481195-82-8 481196-01-4, Adducin gamma subunit (human) 481196-11-6 481196-30-9 481196-49-0 481196-70-7 481196-81-0, Protein (human 177-amino acid) 481196-98-9 481197-01-7 481197-28-8, HMFG (human gene HMFG) 481198-32-7 481198-65-6, Protein (human gene prohibitin) 481198-91-8 481200-09-3, HZF-16.2 (human gene HZF-16) 481200-10-6, HZF-16.1 (human gene HZF-16) 481200-42-4 481200-95-7, TLS (human gene TLS) 481201-13-2, FBRNP (human gene D10S102) 481201-33-6 481201-34-7 481201-67-6 481201-91-6 481202-22-6 481202-29-3 481202-48-6 481202-63-5, APK1 antigen (human gene APK1 antigen) 481202-99-7 481203-70-7 481203-83-2, IK factor (human gene IK) 481203-85-4, E2F-4 (human gene E2F-4) 481204-50-6, AML1 (human gene AML1)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; genes that are differentially expressed during erythropoiesis and their diagnostic and therapeutic uses)

L24 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:851837 HCAPLUS
DOCUMENT NUMBER: 141:104117
TITLE: Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease. [Erratum to document cited in CA136:051990]
AUTHOR(S): MacDonald, Tobey J.; Brown, Kevin M.; LaFleur, Bonnie; Peterson, Katia; Lawlor, Christopher; Chen, Yidong; Packer, Roger J.; Cogen, Philip; Stephan, Dietrich A.
CORPORATE SOURCE: Center for Cancer and Transplantation Biology, Children's National Medical Center, Washington, DC, USA
SOURCE: Nature Genetics (2003), 35(3), 287
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The annotation for the Affymetrix G110 probe set 1770 that was used was incorrect. Although the annotation specifies that the transcript for PDGFR-α is being ascertained, the true specificity of the probe set is for the PDGFR-β isoform. The ligand for both receptor isoforms is identical. The functional validation of the PDGFR signaling pathway, described in our article, used specific neutralizing antibodies against PDGFR-α as well as downstream small mol. inhibitors, and it implicates this entire cascade. The PDGFR-β isoform may be more relevant in the metastatic process, but this does not discount the proven biol. role of PDGFR-α and downstream effectors in metastatic medulloblastoma.
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(MAPKAP kinase-3-encoding; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease (Erratum))
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(N-Shc p52 and p64 isoform-encoding; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease (Erratum))
IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study) (SHC, N-Shc, p52 and p64 isoforms; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease (Erratum))

IT 9013-66-5, Glutathione peroxidase 9025-26-7, Cathepsin D 9032-68-2, Cathepsin C 37353-41-6, Cysteine protease 80449-02-1, Protein tyrosine kinase 86102-31-0, Tissue inhibitor of metalloproteinase 142008-29-5, CAMP-dependent protein kinase 148348-15-6, Keratinocyte growth factor 149885-84-7, Phosphatase, phosphoprotein (phosphoserine/phosphothreonine/phosphotyrosine) 151769-16-3, TNF-α-converting enzyme 161052-08-0, Gene tie protein kinase 167398-03-0, Protein kinase HEK8 170347-54-3, Gene txk protein kinase 175780-17-3, MAPKAP kinase-3 289898-51-7, JNK1 kinase 377752-08-4, Ribosomal S6 kinase 2
RL: BSU (Biological study, unclassified); BIOL (Biological study) (gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease (Erratum))

L24 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:615889 HCAPLUS
DOCUMENT NUMBER: 137:180730
TITLE: Human cDNA/DNA molecules and proteins encoded by them with enhanced expression in apoptosis-resistant cell clones, and use thereof in diagnosis, therapeutics and drug screening
INVENTOR(S): Ullrich, Axel; Abraham, Reimar
PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V., Germany
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002063037	A2	20020815	WO 2002-EP1073		20020201
WO 2002063037	A3	20031002			
WO 2002063037	A9	20040219			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2434881	A1	20020815	CA 2002-2434881		20020201
AU 2002249170	A1	20020819	AU 2002-249170		20020201
AU 2002249170	B2	20070208			
EP 1364066	A2	20031126	EP 2002-718083		20020201
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004517638	T	20040617	JP 2002-562773		20020201
US 2004110177	A1	20040610	US 2003-470845		20030731
AU 2007201963	A1	20070524	AU 2007-201963		20070502
PRIORITY APPLN. INFO.:			US 2001-265631P	P	20010202
			AU 2002-249170	A3	20020201
			WO 2002-EP1073	W	20020201

AB The present invention relates to a method for identifying nucleic acid mols. functionally associated with a desired phenotype, such as cancer cell properties, including anti-apoptosis. The method, which allows for

generation of expression profiles of genes associated with said desired phenotype, involves a mutagenesis and/or genome rearrangement step, followed by selection of cell clones displaying the desired phenotype. The invention also relates that the method involves the use of the following techniques: fluorescence-activated cell sorting (FACS); nucleic acid microarray (cDNA, genomic or oligonucleotide); protein array; two-dimensional gel electrophoresis; and/or mass spectrometry. The invention further relates that the disclosed method was used to identify genes, which are differentially expressed in apoptosis-sensitive and apoptosis-resistant cells. Specifically, the invention relates that apoptosis was induced in human cervix carcinoma cell line HeLa S3 by Fas activation. After the selection procedure, only a low number of living cells were present, which had a higher resistance against apoptosis than the parental cell line. MRNA was isolated from these surviving clones, and from the parental cell line, and transcribed into cDNA. CDNA microarray technol. was used to identify about 150-200 genes (cDNA/DNA mols.) that exhibited enhanced expression in apoptosis-resistant clones. The GenBank accession nos. of some of these cDNA/DNA mols. are provided, along with the products encoded by said mols. Still further, the invention relates that most of the apoptosis-associated genes encode protein phosphatases, and kinases. Finally, the invention relates that said nucleic acid mols., and proteins encoded by mols., can be used as targets in diagnosis, therapeutics and drug screening, particularly for disorders associated with dysfunction of apoptotic processes, such as tumors.

IT Proteins
RL: ANT (Analyte); BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(SHC; identification of proteins (kinases, phosphatases, enzymes, and receptors) with enhanced expression in apoptosis-resistant cell clones, and their use in diagnosis, therapeutics and drug screening)

IT 9001-41-6, Neuroleukin 9001-50-7, Glyceraldehyde-3-phosphate dehydrogenase 9026-43-1, Serine/threonine protein kinase 52660-18-1, Protein kinase ck1 86102-31-0, TIMP 87397-91-9, Thymosin β10 90698-26-3, Ribosomal p70 S6 protein kinase 102925-39-3, β-Adrenergic receptor kinase 124861-55-8, TIMP-2 proteinase inhibitor 127464-60-2, Vascular endothelial growth factor 137632-06-5, Csk tyrosine kinase 137632-07-6, ERK1 protein kinase 140208-22-6, Cdc25B phosphatase 141467-20-1, Wee1 kinase 141760-45-4, Furin 143375-65-9, Cdc2 kinase 144713-50-8, ERK3 protein kinase 145539-86-2, HCK Tyrosine kinase 146279-87-0 146838-20-2, Gene bcr protein kinase 146838-30-4, MAPKAP kinase-2 147302-47-4, Gene trkC protein tyrosine kinase 148640-14-6, RAC protein kinase 149433-91-0, EphA2 receptor tyrosine kinase 150027-19-3, A-Raf-1 kinase 151662-26-9, Tyrosine kinase itk 152478-57-4, JAK2 protein kinase 152743-99-2, ErbB-4 receptor tyrosine kinase 152787-71-8, Protein kinase TTK 153190-46-6, Protein kinase MLK3 153190-61-5, Tyk2 kinase 154907-65-0, Checkpoint kinase Chk1 154907-68-3, Rse protein tyrosine kinase 156621-09-9, MSK1 protein kinase 156859-16-4, Gene ryk protein kinase 158129-99-8, GRK6 receptor kinase 163441-58-5, Hyl tyrosine kinase 165245-99-8, Protein kinase Plk1 169150-71-4, DAP kinase 170347-50-9, FAST kinase 170780-46-8, Protein tyrosine kinase PYK2 172306-41-1, Protein kinase PCTAIRE-1 172306-53-5, Protein kinase LIMK-1 172308-17-7, Matrix metalloproteinase-15 173585-04-1, Integrin-linked kinase 174206-56-5, Gene mnb protein kinase 175780-17-3, MAPKAP kinase 3 176023-60-2, Gene AKT2 protein kinase 176023-62-4, Protein kinase PKN 178037-70-2, Protein kinase SGK 179466-45-6, Protein kinase Ndr 182238-33-1, Gene RON receptor kinase 182372-11-8, Metalloproteinase ADAM12 184049-62-5, Protein phosphatase PYST1 187042-29-1, Cyclin G-associated kinase 188265-45-4, Gene KHS protein kinase 192230-91-4, MAPK kinase 3 193099-10-4, Metalloprotease ADAM15 194739-73-6, MAP kinase kinase 6 195740-69-3, Protein kinase ARK2 197664-51-0, Gene lok protein kinase 200578-48-9, Protein kinase

IRAK-2 202420-94-8, Cdc25C-associated protein kinase 203945-19-1, Protein kinase BUB1 204784-44-1, Protein kinase SRPK2 204934-34-9, EphB3 receptor tyrosine kinase 216974-70-8, EphB4 receptor tyrosine kinase 219575-48-1, Ste20-like kinase 233284-43-0, Gene NEK3 protein kinase 252351-00-1, Metalloprotease ADAM-8 253170-37-5, MSK2 kinase 262450-51-1, Protein kinase MST3 268742-11-6, Protein kinase CHED 300830-60-8, Protein tyrosine phosphatase MEG2 300853-81-0, Protein tyrosine phosphatase ζ 300855-77-0, Protein tyrosine phosphatase 1C 300865-18-3, RPTP-μ 301167-76-0, Protein tyrosine phosphatase CAAX2 327046-95-7, MAP kinase kinase 5 329767-79-5, Protein tyrosine phosphatase σ 335605-46-4, MKK7 protein kinase 335605-46-4, Jun N-terminal kinase kinase 2 352521-00-7, Protein tyrosine phosphatase PRL-3 361186-44-9, Protein phosphatase PP5 362516-16-3, IKKα kinase 366806-33-9, CASEIN KINASE II 408328-74-5, IKKγ kinase 409105-92-6, Protein kinase MAST205 420790-04-1, Pim-2 protein kinase 444993-55-9, Gene VRK1 protein kinase (phosphorylating)
RL: ANT (Analyte); BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(identification of proteins (kinases, phosphatases, enzymes, and receptors) with enhanced expression in apoptosis-resistant cell clones, and their use in diagnosis, therapeutics and drug screening)

L24 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:756373 HCAPLUS
DOCUMENT NUMBER: 136:51990
TITLE: Expression profiling of medulloblastoma: PDGFRA and the RAS/MAPK pathway as therapeutic targets for metastatic disease
AUTHOR(S): MacDonald, Tobey J.; Brown, Kevin M.; LaFleur, Bonnie; Peterson, Katia; Lawlor, Christopher; Chen, Yidong; Packer, Roger J.; Cogen, Philip; Stephan, Dietrich A.
CORPORATE SOURCE: Center for Cancer and Transplantation Biology, Children's National Medical Center, Washington, DC, USA
SOURCE: Nature Genetics (2001), 29(2), 143-152
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Little is known about the genetic regulation of medulloblastoma dissemination, but metastatic medulloblastoma is highly associated with poor outcome. We obtained expression profiles of 23 primary medulloblastomas clin. designated as either metastatic (M+) or non-metastatic (M0) and identified 85 genes whose expression differed significantly between classes. Using a class prediction algorithm based on these genes and a leave-one-out approach, we assigned sample class to these tumors (M+ or M0) with 72% accuracy and to four addnl. independent tumors with 100% accuracy. We also assigned the metastatic medulloblastoma cell line Daoy to the metastatic class. Notably, platelet-derived growth factor receptor α (PDGFRA) and members of the downstream RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway are upregulated in M+ tumors. Immunohistochem. validation on an independent set of tumors shows significant overexpression of PDGFRA in M+ tumors compared to M0 tumors. Using in vitro assays, we show that platelet-derived growth factor α (PDGFA) enhances medulloblastoma migration and increases downstream MAP2K1 (MEK1), MAP2K2 (MEK2), MAPK1 (p42 MAPK) and MAPK3 (p44 MAPK) phosphorylation in a dose-dependent manner. Neutralizing antibodies to PDGFRA blocks MAP2K1, MAP2K2 and MAPK1/3 phosphorylation, whereas U0126, a highly specific inhibitor of MAP2K1 and MAP2K2, also blocks MAPK1/3. Both inhibit migration and prevent PDGFA-stimulated migration. These results provide the first insight into the genetic regulation of medulloblastoma metastasis and are the first to suggest a role for PDGFRA and the RAS/MAPK signaling pathway in medulloblastoma metastasis. Inhibitors of PDGFRA and

RAS proteins should therefore be considered for investigation as possible novel therapeutic strategies against medulloblastoma.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(MAPKAP kinase-3-encoding; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(N-Shc p52 and p64 isoform-encoding; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SHC, N-Shc, p52 and p64 isoforms; gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease)

IT 9013-66-5, Glutathione peroxidase 9025-26-7, Cathepsin D 9032-68-2, Cathepsin C 37353-41-6, Cysteine protease 80449-02-1, Protein tyrosine kinase 86102-31-0, Tissue inhibitor of metalloproteinase 142008-29-5, CAMP-dependent protein kinase 148348-15-6, Fibroblast growth factor 7 149885-84-7 151769-16-3, TNF-α-converting enzyme 161052-08-0, Gene tie protein kinase 167398-03-0, Protein kinase HEK8 170347-54-3, Gene txk protein kinase 175780-17-3, MAPKAP kinase-3 289898-51-7, JNK1 kinase 377752-08-4, Ribosomal S6 kinase 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression profiling of medulloblastoma and PDGFRA and RAS/MAPK pathway as therapeutic targets for metastatic disease)

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(FILE 'HOME' ENTERED AT 07:41:14 ON 02 AUG 2007)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, HCAPLUS, NTIS, LIFESCI' ENTERED AT 07:41:51 ON 02 AUG 2007

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L1      12209 S "SHC"
L2      17027 S SH3 (W)DOMAIN
L3        588 S L1 AND L2
L4       2640 S "MAPKAP2 KINASE?" OR "MK2"
L5          0 S L3 AND L4
L6       2372 S MAPKAP####
L7          1 S L3 AND L6
L8          5 S L1 AND L4
L9          2 DUP REM L8 (3 DUPLICATES REMOVED)
L10     12209 S "SHC#"
L11       312 S KINASE(W) BINDING (W)DOMAIN?
L12         6 S L1 AND L11
L13         1 DUP REM L12 (5 DUPLICATES REMOVED)
L14        13 S L4 AND (PROLINE (W)RICH)
L15         3 DUP REM L14 (10 DUPLICATES REMOVED)
L16         0 S L4 (3W)TRAGET?
L17         0 S L6 (2W)TRAGET?
L18         2 S L6 (2W)TARGET?
L19        44 S L4 (3W)TARGET?
L20         0 S L19 AND L10
L21         9 DUP REM L19 (35 DUPLICATES REMOVED)
L22         0 S L4 AND "66K##"
L23        13 S L10 AND (L6 OR L4)
L24        10 DUP REM L23 (3 DUPLICATES REMOVED)
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